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UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF CALIFORNIA

RALPH COLEMAN, et al.,

Plaintiffs,

v.

GAVIN NEWSOM, et al.,

Defendants.

Case No. 2:90-CV-00520-KJM-DB

PLAINTIFFS' BRIEF RE: EVIDENCE SUPPORTING SERIOUS MENTAL ILLNESS AS RISK FACTOR FOR COVID-19 AND NEED FOR ADDITIONAL MENTAL HEALTH INTERVENTIONS

Judge: Hon. Kimberly J. Mueller
Crtrm.: 3, 15th Floor, Sacramento

TABLE OF CONTENTS

Page

INTRODUCTION

At the June 12, 2020 COVID-19 status conference, the Court asked whether Defendants were aware of guidance specific to treating and managing the risk of COVID-19 in the mentally ill incarcerated population. *See* Tr., ECF No. 6722 at 19 (June 16, 2020). In response, Dr. Joseph Bick, Director of Health Care Services for CDCR, stated that there was no such guidance, and also that there has not been "evidence for adverse outcomes specifically related to the mental health of clients." *Id.* at 20.; *see id.* at 20-21. Dr. Bick went on to state that he did not "believe there are specific strategies that need to be developed regarding our mentally ill patients" with respect to managing their COVID-19 risk. *Id.* at 21. Notwithstanding the foregoing, Dr. Bick acknowledged "that for many of our patients, including the mentally ill, … there are particular challenges to them maintaining hygiene and following the guidance that we're providing but nothing that I've seen [] is specific to the mental health patients." *Id.*

On June 19, 2020, in response to the Court's question and Dr. Bick's assertions at the June 12 status conference, Plaintiffs shared with Defendants and the Special Master team a letter collecting dozens of readily available scientific sources that identify serious mental illness ("SMI") as a risk factor for COVID-19. *See* Decl. of Michael W. Bien in Supp. of Pls' Br. Re: Evidence Supporting SMI as Risk Factor for COVID-19 & Need for Add'l Mental Health Interventions, filed herewith ("Bien Decl."), at ¶ 10. Those sources describe an increased risk in the SMI population of both COVID-19 infection and adverse outcomes, along with the need for additional mental health interventions for the SMI population during the COVID-19 pandemic. *See generally* Sections I, II, & III, *infra*. Plaintiffs also explained the need to rely on analogous medical or behavioral conditions, along with common sense, to inform CDCR's COVID-19 response, in light of the novelty of the pandemic and lack of time to conduct carefully controlled scientific studies. Bien Decl., at ¶ 10; *see also* Decl. of Robert M. Sapolsky, Ph.D., *Arevalo v. Decker*, No. 1:20-cv-02982, Dkt. 3-3 (S.D.N.Y. Apr. 13, 2020), attached to Bien Decl. as **Exhibit 29** (explaining that in the absence of COVID-19-specific research, mental health impacts on

COVID-19 infections can be extrapolated with "considerable confidence" from existing science). Because of the lack of scientific guidance specific to COVID-19, a novel coronavirus, these same approaches have been used proactively in the larger community since the very beginning of the pandemic to manage the public health crisis. The parties, under the supervision of the Special Master, briefly discussed these issues at the June 23, 2020 COVID-19 taskforce meeting. *Id.* at ¶ 10.

Plaintiffs informed the Court at the June 26, 2020 COVID-19 status conference of the materials provided to Defendants and the Special Master. *Id.* at ¶ 10. Defendants confirmed that additional discussions and work were necessary in light of the materials Plaintiffs had provided. *Id.* at ¶ 10. The Court thereafter invited the parties to file pleadings and the supporting evidence of publications showing that SMI is a risk factor for COVID-19.

Accordingly, Plaintiffs have described below and provided as exhibits guidance specific to managing COVID-19 risk in SMI and/or closely related populations, along with findings demonstrating the need for additional mental health interventions to deal with the impacts of social distancing and other major lifestyle changes resulting from the pandemic. Plaintiffs also include herein some recently discovered additional studies and guidance that have not previously been provided to Defendants and the Special Master given the rapidly evolving understanding of the novel virus.

I. SMI Is Well-Established as a COVID-19 Risk Factor.

SMI's status as a COVID-19 risk factor is well-established, both directly and by analogy to similar conditions. *See generally* Section II, *infra*. Recently, this correlation has been shown to play out dangerously in both national data and in the CDCR population.

On June 15, 2020, the Centers for Disease Control and Prevention ("CDC") published a statistical analysis of all COVID-19 cases that had been reported to the agency between January 22 and May 30, 2020. *See* CDC, *Morbidity and Mortality Weekly Report: Coronavirus Disease 2019 Case Surveillance – United States, January 22-May 30, 2020*, Vol. 69 (June 15, 2020), attached to Bien Decl. as **Exhibit 2**. The CDC identified a

number of underlying health conditions that lead to increased COVID-19 risk of adverse outcomes, including psychological and psychiatric conditions. *See id.* at 4, Tbl. 2 & n.*. Critically, individuals in the CDC study who had at least one underlying health condition were six times more likely to be hospitalized (45% versus 7.6%), and 12 times more likely to die (19.5% versus 1.6%) from a COVID-19 infection. CDC, *Morbidity and Mortality Weekly Report: Coronavirus Disease 2019 Case Surveillance – United States, January 22-May 30, 2020*, Vol. 69 at 1, 4, 6 (June 15, 2020), attached to Bien Decl. as **Exhibit 2**.

The SMI population also tends to experience other high-risk underlying health conditions at a disproportionately high rate, caused, at least in part, by common side effects of psychotropic medications. *Compare id.*, *with* Ann K. Shinn, et al., *Perspectives on the COVID-19 Pandemic and Individuals with Serious Mental Illness*, Journal of Clinical Psychiatry (Apr. 28, 2020), attached to Bien Decl. as **Exhibit 31** (identifying cardiovascular disease, obesity, metabolic syndrome, diabetes, and respiratory conditions as comorbidities correlated with SMI and/or the use of psychotropic medications to treat SMI); Jeffrey L. Geller, et al., *Patients with SMI in the Age of COVID-19: What Psychiatrists Need to Know*, Psychiatric News (Apr. 7, 2020), attached to Bien Decl. as **Exhibit 30** (same).

According to the CDC study, older adults are far more likely to contract COVID-19 than average and are also far more likely to be hospitalized and die. *See id.*; Bien Decl., at ¶¶ 5-8. While the overall incidence of infection was 403 cases per 100,000, the per-100,000 incidence for people ages 70-79 was 464, and the incidence for people age 80 and older was 902. *See* Bien Decl., at ¶ 8 & **Exhibit 2**. Overall, 14% of all infected patients were hospitalized, 2% admitted to ICU, and 5% died, while 28% of patients who were age 80 and over died. *See id.* And 50% of those 80 years or older with at least one underlying health condition died as a result of their infection (as compared to 30% of those without an underlying condition). *See id.*

Plaintiffs' recent data analysis confirms the trends in the CDCR population are paralleling the national trends. *See* Bien Decl., at ¶¶ 2-4 & **Exhibit 1**. Specifically, data

from CDCR's COVID-19 Registry as of July 1, 2020 at approximately 8:36 am showed 4,808 active or resolved cases (excluding patients deceased or released) among incarcerated patients. *Id.* at ¶ 3. *Coleman* class members made up 40% of those hospitalized, and the mean age of hospitalized patients was 61.3 years-old (median 61.5 years-old). *Id.* at ¶ 4. Of those who have died from COVID-19 in CDCR, 50% were *Coleman* class members at the time of their death or were recent former participants in the Mental Health Services Delivery System. *Id.* The mean age of patients who have died from COVID-19 in CDCR custody is 62.6 years-old. *Id.* All of the patients who died were either 55 or older, a *Coleman*, *Armstrong* or *Clark* class member, or designated high-risk medical. *Id.* A recent twenty-third decedent, whose cause of death CDCR has not yet been confirmed but who tested positive for COVID-19, was a 71-year-old *Coleman* and *Armstrong* class member. COVID-19 is an equal opportunity killer, but those with underlying health conditions, including SMI and other disabilities, experience starkly different outcomes than those without such conditions.

II. Two Common Characteristics of the SMI Population Lead to Their Increased Risk of Both Contracting COVID-19 and Experiencing a Poor Outcome, Including Death, from a COVID-19 Infection, and Available Data Shows These Characteristics Are Prevalent in the *Coleman* Class.

Two aspects of SMI are likely to contribute significantly to the greater risk class members experience both in rates of COVID-19 infection and poor outcomes from infection. First, individuals with SMI often have functional limitations or engage in behaviors that increase the likelihood of transmission and/or the severity of the disease once infected. Second, individuals with SMI have a high rate of medical comorbidities that lead to more and more severe complications, and poor ultimate outcomes, from COVID-19 infection. At least some of these comorbidities are caused by the use of psychotropic medications to treat various mental illnesses.

A. Those with SMI typically engage in behaviors or have functional limitations that make it harder to engage in infection control practices like social distancing, and are therefore more likely to contract COVID-19.

Those with SMI, like other groups with behavioral differences and functional limitations, are less likely to be able to understand and/or benefit from basic infection control practices critical to stemming the spread of COVID-19. Specifically, individuals with certain forms or expressions of mental illness will typically find social distancing, handwashing, mask-wearing, and other COVID-19 infection avoidance strategies very challenging. They may not understand social distancing and similar requirements, or simply may not be able to comply with those requirements, at least on a consistent basis. These tendencies are well-documented and various governmental and scientific sources have advised that these differences must be taken into account in caring for people with SMI and similarly situated populations.

For example, the Department of Health and Human Services has issued guidance to healthcare facilities, including psychiatric facilities, for infection control considerations specific to the SMI and those with similar functional limitations. *See* Department of Health & Human Services, Centers for Medicare and Medicaid Services, March 30, 2020: *Guidance for Infection Control and Prevention of Coronavirus Disease (COVID-19) in Hospitals, Psychiatric Hospitals, and Critical Access Hospitals (CAHs): FAQs, Considerations for Patient Triage, Placement, Limits to Visitation and Availability of 1135 waivers*, attached to Bien Decl. as **Exhibit 3**, at 8 ("Special consideration should be given to patients with psychiatric or cognitive disabilities to ensure they are able to adhere to the COVID-19 discharge recommendations and fully comprehend the significance of the precautions, or they have a family member or significant other involved to assist with these restrictions."); *cf.* Department of Health & Human Services, Centers for Medicare and Medicaid Services, March 30, 2020: *Guidance for Infection Control and Prevention of Coronavirus Disease 2019 (COVID-19) in Intermediate Care Facilities for Individuals with Intellectual Disabilities (ICF/IIDs) and Psychiatric Residential Treatment Facilities*

(PRTFs), attached to Bien Decl. as **Exhibit 4** ("Facilities should adhere to the infection prevention and control practices issued by the CDC. It may be appropriate to consult with your state health agency for guidance based on the unique challenges of instituting infection prevention and control with individuals with intellectual disabilities in an ICF/IID.").

The CDC has acknowledged this issue as well, *see* CDC, *Coronavirus Disease 2019 (COVID-19): People with Disabilities*, attached to Bien Decl. as **Exhibit 5** (explaining that individuals in certain disability categories may "be at increased risk of becoming infected or having unrecognized illness"; the categories include "[p]eople who have trouble understanding information or practicing preventative measures, such as hand washing and social distancing"), as have numerous scientific publications, *see* Ann K. Shinn, et al., *Perspectives on the COVID-19 Pandemic and Individuals with Serious Mental Illness*, Journal of Clinical Psychiatry (Apr. 28, 2020), attached to Bien Decl. as **Exhibit 31** (explaining that features of SMI "may make it harder for people with SMI to find accurate information about COVID-19 and to organize, appraise, and translate health information into behavior that reduces risk of exposure and infection," and noting factors that contribute to poor health outcomes for individuals with SMI include typical delays in accessing medical treatment, difficulty recognizing and reporting medical symptoms, and lower rates of adherence to treatment for medical conditions); *COVID-19 Can Have Serious Effects on People with Mental Health Disorders*, Healthline (Apr. 7, 2020), attached to Bien Decl. as **Exhibit 6** (linking SMI and COVID-19 risk due to a number of behavioral and functional factors: typical congregate living situations, substance abuse, limits on ability or understanding of the need for self-care and social distancing; and a tendency to delay in seeking out medical treatment); Nicole M. Benson, et al., *COVID-19 Testing and Patients in Mental Health Facilities* (May 11, 2020), attached to Bien Decl. as **Exhibit 8** (explaining that management of COVID-19 may be challenging for individuals with psychiatric disorders due to their inability to adhere to recommendations like physical distancing and frequent handwashing); Jeffrey L. Geller, et al., *Patients with SMI in the*

Age of COVID-19: What Psychiatrists Need to Know, Psychiatric News (Apr. 7, 2020), attached to Bien Decl. as **Exhibit 30** (cognitive deficits, mental disorganization, and similar features of mental illness will play a role in SMI individuals' understanding of the disease and necessary steps for hygiene and prevention; physiological and other expressions of anxiety disorders, like panic attacks, may make it difficult for mentally ill individuals to identify COVID-19 symptoms and may lead to over- or under-reporting of symptoms; and for various other reasons, people with SMI may delay in seeking out medical care); *cf.* Andrea Fiorillo et al., *Psychosocial interventions to reduce premature mortality in patients with serious mental illness* (May 15, 2020), attached to Bien Decl. as **Exhibit 9** (recommending a psychosocial approach to treating behavioral differences in SMI individuals that lead to higher mortality rates); Joseph Shapiro, *COVID-19 Infections and Deaths Are Higher Among Those with Intellectual Disabilities* (June 9, 2020), attached to Bien Decl. as **Exhibit 10** (finding that people with intellectual or developmental disabilities have risks two or more times greater both of contracting COVID-19 and having poor outcomes from an infection); Marla Milling, *People with Intellectual and Developmental Disabilities More Likely to Die from COVID-19* (May 28, 2020), attached to Bien Decl. as **Exhibit 11** (describing same); CDC, *People with Developmental and Behavioral Disabilities* (May 27, 2020), attached to Bien Decl. as **Exhibit 36** ("Some people with developmental or behavioral disorders may have difficulties accessing information, understanding or practicing preventative measures, and communicating symptoms of illness."); Alzheimer's Association, *Coronavirus (COVID-19): Tips for Dementia Caregivers*, attached to Bien Decl. as **Exhibit 12** ("Most likely, dementia does not increase risk for COVID-19 … just like dementia does not increase risk for flu. However, dementia-related behaviors, increased age and common health conditions that often accompany dementia may increase risk. For example, people with Alzheimer's disease and all other dementia may forget to wash their hands or take other recommended precautions to prevent illness.").

Given the abundant, consistent guidance on this point, Plaintiffs have requested that

Defendants develop additional policies, training, and procedures for managing COVID-19 prevention for the *Coleman* class.

B. People with serious mentally illness have significantly higher rates of comorbid medical conditions that place them at greater risk for COVID-19 infection and poor outcomes than do those without mental illness.

Unfortunately, it is well established that people with SMI tend also to be at higher risk for medical comorbidities or otherwise are particularly vulnerable to COVID-19 infection and/or serious complications arising therefrom. *See, e.g.*, World Health Organization, *Management of Physical Health Conditions in Adults with Severe Mental Disorders*, at 60 (2018), attached to Bien Decl. as **Exhibit 13** ("People with [SMI] are at greater risk than the general population for exposure to infectious diseases"); *id.* at 10, 61 (noting "the association between [SMI] and infectious diseases" and that infectious diseases "contribute to the high rates of premature death amongst people with [SMI]"); Jeffrey L. Geller, et al., *Patients with SMI in the Age of COVID-19: What Psychiatrists Need to Know*, Psychiatric News (Apr. 7, 2020), attached to Bien Decl. as **Exhibit 30** ("Patients with SMI are particularly vulnerable to COVID-19 due to generally being in worse physical health than the general population. They typically … have more medical comorbidities such as hypertension and diabetes. In addition to the widely recognized risk factors for COVID-19—diabetes, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD)—the American College of Cardiology also identified obesity and hypertension as risk factors for viral respiratory illnesses, including COVID-19. CVD and its risk factors—psychotic illness being an independent risk factor for CVD—are twice as high in patients with schizophrenia than in the general population. Likewise, obesity is twice as prevalent and diabetes is at least three times as prevalent in people with SMI compared with the nonpsychiatric population in all age groups."); *COVID-19 Can Have Serious Effects on People with Mental Health Disorders*, Healthline (Apr. 7, 2020), attached to Bien Decl. as **Exhibit 6** (noting the increased risk of comorbidities that impact respiratory function or otherwise make seriously mentally ill

individuals more susceptible to COVID-19 and adverse outcomes therefrom); Matthew J. Akiyama, M.D., et al., *Flattening the Curve for Incarcerated Populations – COVID-19 in Jails and Prisons*, New England Journal of Medicine (May 28, 2020), attached to Bien Decl. as **Exhibit 14** (identifying mental illness as one social determinant that impacts physical health at a greater proportion in incarcerated populations and therefore leads to an increased COVID-19 risk in these settings); Nicole M. Benson, et al., *COVID-19 Testing and Patients in Mental Health Facilities* (May 11, 2020), attached to Bien Decl. as **Exhibit 8** ("[Patients in mental health facilities] are at higher risk for complications of COVID-19 because they frequently have underlying medical conditions that worsen their prognosis (*e.g.*, cardiac disease, history of smoking)."); Andrea Fiorillo et al., *Psychosocial interventions to reduce premature mortality in patients with serious mental illness* (May 15, 2020), attached to Bien Decl. as **Exhibit 9** ("Compared with the general population, patients with serious mental illness (SMI), *i.e.*, schizophrenia, major depression, and bipolar disorders, have higher levels of morbidity, poorer health outcomes, and higher mortality rates.[] In particular, life expectancy is reduced up to 25 years.[] The causes of this premature mortality have been extensively analyzed, and the vast majority is due to the higher incidence of physical health problems, such as cancer as well as cardiovascular, respiratory, metabolic, and infectious diseases."); Ann K. Shinn, et al., *Perspectives on the COVID-19 Pandemic and Individuals with Serious Mental Illness*, Journal of Clinical Psychiatry (Apr. 28, 2020), attached to Bien Decl. as **Exhibit 31** (explaining that even without COVID-19, individuals with SMI have 3.7 times the mortality rate than the general population, largely due to cardiovascular and respiratory diseases); *Open Letter to ICE from Medical Professionals Regarding COVID-19*, at 2 (Mar. 13, 2020), attached to Bien Decl. as **Exhibit 15** (identifying SMI individuals as particularly vulnerable to COVID-19 infection); Decl. of Robert M. Sapolsky, Ph.D., *Arevalo v. Decker*, No. 1:20-cv-02982, Dkt. 3-3 (S.D.N.Y. Apr. 13, 2020), attached to Bien Decl. as **Exhibit 29** (chronic stress and related mental health conditions have medical impacts including depression of the immune system, leading to vulnerability to infectious viruses like

COVID-19 and ensuing disease; Type II diabetes; obesity; hypertension; inflammation of the lungs or other body systems; and cardiovascular disease); *cf.* Laura M. Maruschak et al., *Pandemic Influenza and Jail Facilities and Populations*, 99 Am. J. Public Health (2009) at S339-44 attached to Bien Decl. as **Exhibit 16** (partially as a result of higher rates of mental illness, incarcerated individuals are "particularly vulnerable" to influenza pandemics); Department of Health & Human Services, Centers for Medicare and Medicaid Services, March 30, 2020: *Guidance for Infection Control and Prevention of Coronavirus Disease 2019 (COVID-19) in Intermediate Care Facilities for Individuals with Intellectual Disabilities (ICF/IIDs) and Psychiatric Residential Treatment Facilities (PRTFs)*, attached to Bien Decl. as **Exhibit 4** at 3 (noting "the high infection rate of COVID-19 and the increased vulnerability of people with disabilities to have serious response[s] due to complications"); CDC, *Coronavirus Disease 2019 (COVID-19): People with Disabilities*, attached to Bien Decl. as **Exhibit 5** ("Adults with disabilities are three times more likely than adults without disabilities to have heart disease, stroke, diabetes, or cancer than adults without disabilities.").

The increased risk of medical comorbidities may be due at least in part to the side effects of psychotropic medications used to treat SMI. Jeffrey L. Geller, et al., *Patients with SMI in the Age of COVID-19: What Psychiatrists Need to Know*, Psychiatric News (Apr. 7, 2020), attached to Bien Decl. as **Exhibit 30** (antipsychotic medications tend to increase obesity, metabolic syndrome, diabetes, and cardiovascular symptoms, and certain other psychotropic medications tend to depress respiratory function); Ann K. Shinn, et al., *Perspectives on the COVID-19 Pandemic and Individuals with Serious Mental Illness*, Journal of Clinical Psychiatry (Apr. 28, 2020), attached to Bien Decl. as **Exhibit 31** (psychotropic medications can lead to increased risk of diabetes and cardiovascular disease).

Below are references to scientific articles that describe the relationship between common mental health conditions and the types of comorbid medical conditions that place people with SMI at higher risk for COVID-19 infection and adverse outcomes:

- **Anxiety:** Catherine Kariuki-Nyuthea et al., *Anxiety and Related Disorders and Physical Illness*, 179 Comorbidity of Mental and Physical Disorders 81 (2015), at 82, 85, attached to Bien Decl. as **Exhibit 17** (describing "a growing body of evidence for a strong bidirectional association between anxiety and related disorders and co-occurring general medical conditions," including respiratory illnesses; association resulting in part from fact that "anxiety and related disorders may lead to vulnerability for various medical conditions").

- **Bipolar Disorder:** Joshua D. Rosenblat & Roger S. McIntyre, *Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications*, 7 Brain Sci. 144 (2017), at 1, 11, attached to Bien Decl. as **Exhibit 18** ("Bipolar disorder (BD) is strongly associated with immune dysfunction. Replicated epidemiological studies have demonstrated that BD has high rates of inflammatory medical comorbidities, including autoimmune disorders, chronic infections, cardiovascular disease and metabolic disorders.").

- **Depression:** Janice K. Kiecolt-Glasera et al., *Depression and immune function: Central pathways to morbidity and mortality*, 53 Journal of Psychosomatic Research (2002), at 873, 875, attached to Bien Decl. as **Exhibit 19** (depression "directly prompts immune dysregulation," "may lead to subsequent maladaptive immune and endocrine changes," and "may also contribute to prolonged infection"); American Psychological Association, *Stress Weakens the Immune System*, attached to Bien Decl. as **Exhibit 20** ("[D]epression hurts immunity; it's also linked to other physical problems such as heart disease.").

- **Posttraumatic Stress Disorder:** Gretchen N. Neigh et al., *Co-Morbidity of PTSD and Immune System Dysfunction: Opportunities for Treatment*, 29 Curr. Opin. Pharmacol. 104 at 2 (2016), attached to Bien Decl. as **Exhibit 21** ("PTSD is associated with poor self-reported physical health as well as high rates of comorbidities, such as cardiovascular, respiratory, gastrointestinal, inflammatory and autoimmune diseases.")

- **Schizophrenia:** Sukanta Saha et al., *A Systematic Review of Mortality in Schizophrenia. Is the Differential Mortality Gap Worsening Over Time?*, 64 Arch. Gen. Psych. 1123, 1125 & Fig. 1, Tbl. 1 (2007), attached to Bien Decl. as **Exhibit 22** (explaining that "people with schizophrenia had 2.5 times the risk of dying compared with the general population," including 3.1 times the risk of dying from respiratory diseases).

- **Stress:** American Psychological Association, *Stress Weakens the Immune System*, attached to Bien Decl. as **Exhibit 20** (citing S.C. Segerstrom & G.E. Miller, *Psychological Stress and the Human Immune System: A Meta-Analytic Study of 30 Years of Inquiry*, Psychological Bulletin, Vol. 130, No. 4 (2004)) ("For stress of any significant duration—from a few days to a few months or years, as happens in real life—all aspects of immunity went downhill. Thus long-term or chronic stress, through too much wear and tear, can ravage the immune system."); Decl. of Robert M. Sapolsky, Ph.D., *Arevalo v. Decker*, No. 1:20-cv-02982, Dkt. 3-3 (S.D.N.Y. Apr. 13, 2020), attached to Bien Decl. as **Exhibit 29** (chronic stress has medical impacts including depression of the immune system, leading to vulnerability to infectious viruses like COVID-19 and ensuing disease; Type II diabetes; obesity; hypertension; inflammation of the lungs or other body systems; and cardiovascular disease).

C. CDCR's data shows that the *Coleman* Class, as is typical of SMI populations, has high rates of medical comorbidities that place them at heightened risk of COVID-19 infection and poor outcomes.

The *Plata* Receiver has confirmed that the trends described above do, indeed, play out in the *Coleman* population. Data provided to Plaintiffs in April shows that *Coleman* class members are roughly 50% more likely to have at least one COVID-19 risk factor than their non-*Coleman* counterparts. *See* Decl. of Donald Specter in Supp. of Pls' Reply Br., ECF No. 6559, Exhibit B, Page 17 (Apr. 1, 2020). Roughly a third of the *Coleman* class is 50 years or older, *see* Decl. of Michael W. Bien in Supp. of Pls' Emergency Motion to Modify Population Reduction Order, ECF No. 6529, at ¶ 55 (Mar. 25, 2020), and age is a significant risk factor for COVID-19, *see* CDC, *Morbidity and Mortality Weekly Report: Coronavirus Disease 2019 Case Surveillance – United States, January 22-May 30, 2020*, Vol. 69 at 1, 4, 6 (June 15, 2020), attached to Bien Decl. as **Exhibit 2**. *Coleman* class members are typical of the larger population of people with SMI, with high rates of medical comorbidities that both render them particularly susceptible to COVID-19 and make COVID-19 particularly dangerous to them.

Coleman class members are at significantly increased risk for COVID-19 infection and resulting severe complications. CDCR's experience with hospitalizations and deaths among class members is consistent with the available scientific information regarding these types of poor outcomes, but CDCR's current policies and practices do not appear to take this information into account. Plaintiffs have urged Defendants to reallocate resources and attention to save more lives by focusing on those—like *Coleman* class members—who have dramatically increased risk of contracting COVID-19 and of experiencing adverse outcomes, including hospitalization and death due to COVID-19, but have not seen significant efforts in this respect to date.

III. Defendants Must Develop a Plan to Address and Treat the Increased Stress and Anxiety Associated with the Pandemic on Underlying Emotional and Psychological Conditions at the Same Time that They Plan to Restore Mental Health Care to Meet Program Guide Standards.

Defendants are obligated to restore mental health care to Program Guide levels as

soon as possible and must prepare additional strategies to address current class members' and non-class members' heightened mental health needs during the pandemic.

A. *Coleman* class members are likely to experience new or increased symptoms as a result of the pandemic and interventions to address the same, and non-class members are likely to experience mental health symptoms for the same reasons.

Due to their pre-existing mental health conditions, class members are more vulnerable than most populations to the mental health impacts caused by the isolation, changes in daily structure and routine, and other social changes arising from the pandemic. *See* Benjamin G. Druss, *Addressing the COVID-19 Pandemic in Populations with Serious Mental Illness* (Apr. 3, 2020), attached to Bien Decl. as **Exhibit 7** ("It will also be important to address the psychological and social dimensions of this epidemic for patients. Worry could both exacerbate and be exacerbated by existing anxiety and depressive symptoms. Physical distancing strategies critical for mitigating the spread of disease may also increase the risk of loneliness and isolation in this population. Those who become ill may face dual stigma associated with their infections and their mental health conditions."); Jeffrey L. Geller, et al., *Patients with SMI in the Age of COVID-19: What Psychiatrists Need to Know*, Psychiatric News (Apr. 7, 2020), attached to Bien Decl. as **Exhibit 30** (noting severe impacts of increased isolation on those with pre-existing mental health conditions); Ann K. Shinn, et al., *Perspectives on the COVID-19 Pandemic and Individuals with Serious Mental Illness*, Journal of Clinical Psychiatry (Apr. 28, 2020), attached to Bien Decl. as **Exhibit 31** ("For people with psychotic disorders, the current circumstances may exacerbate feelings of perplexity, anxiety, and paranoia and may also become integrated into the content of delusions. … The pervasive uncertainty about what to expect and how long the shutdown will last is a major source of distress for many."; "[For some with SMI], isolation measures further reduce and collapse social networks, which are often already tenuous. … Simple but meaningful daytime routines …. are now impossible.").

Due to the stress and isolation resulting from the pandemic and associated

interventions, it is quite likely that incarcerated persons who were not previously class members may require mental health services and support, and may present with SMI. *See generally id.* Individuals with or without pre-existing mental health conditions may also experience medical complications or physiological changes from COVID-19 that create or exacerbate mental health conditions. *See* Aravinthan Varatharaj et al., *Neurological and Neuropsychiatric Complications of COVID-19 in 153 Patients: A UK-Wide Surveillance Study*, The Lancet (June 25, 2020), attached to Bien Decl. as **Exhibit 34** (noting altered mental status as an outcome of COVID-19 complications, including psychosis, dementia-like conditions, and affective, or mood, disorders).

Putting aside their particular vulnerability to COVID-19, many class members now find themselves in near-total lockdown, resembling solitary confinement, further exacerbating their pre-existing conditions. *See, e.g.*, Keramet Reiter, et al., *Psychological Distress in Solitary Confinement: Symptoms, Severity, and Prevalence in the United States*, 2017-2018, 110 Am J. Public Health (Jan. 1, 2020), attached to Bien Decl. as **Exhibit 23** (describing negative mental health impacts of the solitary confinement and segregation settings); Jeffrey L. Metzner et al., *Solitary Confinement and Mental Illness in U.S. Prisons: A Challenge for Medical Ethics*, 38 J. of the Am. Academy of Psychiatry and the Law 104, 104 (2010), attached to Bien Decl. as **Exhibit 24** (same); Brief of Amici Curiae Professors and Practitioners of Psychiatry and Psychology in Support of Petitioner, *Prieto v. Clarke*, No. 15-31, 2015 WL 4720278 (U.S. Aug. 5, 2015), attached to Bien Decl. as **Exhibit 25** (same); Craig Haney, *The Psychological Effects of Solitary Confinement: A Systematic Critique*, 47 Crime and Justice 365, 368, 374 (2018), attached to Bien Decl. as **Exhibit 26** (same); Stuart Grassian, *Psychiatric Effects of Solitary Confinement*, 22 Wash. U. J. L. & Policy 325, 330-32 (2006), attached to Bien Decl. as **Exhibit 27** (same); Jeffrey L. Geller, et al., *Patients with SMI in the Age of COVID-19: What Psychiatrists Need to Know*, Psychiatric News (Apr. 7, 2020), attached to Bien Decl. as **Exhibit 30** ("During this pandemic, it is reasonable to expect that new cases of SMI will arise and need to be addressed by the psychiatric workforce."; "[B]eyond fear of, exposure to, or

actual infection by coronavirus producing psychiatric symptoms, the act of quarantine and isolation itself induces psychiatric symptoms."; "Increased restrictions and overcrowding lead to behavioral outbursts …."); AMEND: Changing Correctional Culture, *The Ethical Use of Medical Isolation – Not Solitary Confinement – to Reduce COVID-19 Transmission in Correctional Settings*, attached to Bien Decl. as **Exhibit 33** ("Research shows that keeping people socially isolated in a closed cell without a meaningful opportunity to communicate with family, friends, and loved ones or to participate in exercise, educational, and rehabilitative programming (solitary confinement) causes immense, and often irreparable, psychological harm.").

Given the pandemic-induced isolation, increased stress, and far-reaching impacts to daily life experienced by incarcerated people in CDCR, it is likely that the need for mental health services—for current class members and non-class members alike—will only increase as the months and possibly years of the pandemic wear on.

B. Defendants must take affirmative steps to provide additional mental health and supportive services during the pandemic.

Since Defendants, like the larger nation, are no longer in the initial crisis management phase of the pandemic, the next step must be to look to, and plan for, the long road ahead. Tangible impacts of the pandemic on daily prison life and the provision of mental health care are now an indefinite reality. Plaintiffs have urged Defendants not only to devise solutions for the delivery of basic mental health care that has been discontinued or curtailed due to their temporary COVID-19 policies, but also to take into account the additional demand for mental health services from both existing class members and the remainder of the population.

Clinicians can do more to educate class members on COVID-19 prevention strategies through in-cell activities, counselling by non-clinical staff, and discussions in clinical groups, individual sessions, and IDTTs, and educational materials should be tailored to the *Coleman* class and others with limited health literacy or particular challenges in implementing prevention strategies like social distancing. *See* Department of

Health & Human Services, Centers for Medicare and Medicaid Services, March 30, 2020: *Guidance for Infection Control and Prevention of Coronavirus Disease 2019 (COVID-19) in Intermediate Care Facilities for Individuals with Intellectual Disabilities (ICF/IIDs) and Psychiatric Residential Treatment Facilities (PRTFs)*, attached to Bien Decl. as **Exhibit 4** at 1-2 (advising health care providers treating those in residential psychiatric facilities to take specific, tailored steps to communicate and educate patients regarding infection control practices, including hygiene); Benjamin G. Druss, *Addressing the COVID-19 Pandemic in Populations with Serious Mental Illness* (Apr. 3, 2020), attached to Bien Decl. as **Exhibit 7** ("People with serious mental illnesses should be provided with up-to-date, accurate information about strategies for mitigating risk and knowing when to seek medical treatment for COVID-19. Patient-facing materials developed for general populations will need to be tailored to address limited health literacy and challenges in implementing physical distancing recommendations …. Patients will need support in maintaining healthy habits, including diet and physical activity, as well as self-management of chronic mental and physical health conditions."); Ann K. Shinn, et al., *Perspectives on the COVID-19 Pandemic and Individuals with Serious Mental Illness*, Journal of Clinical Psychiatry (Apr. 28, 2020), attached to Bien Decl. as **Exhibit 31** (explaining that people with SMI need additional discussion with medical and mental health providers to help understand the risks and benefits of mental health and medical treatment, and that providers must increase communication and relationship-building efforts overall); *cf.* CDC, *Preparing for Coronavirus in Nursing Homes* (June 25, 2020), attached to Bien Decl. as **Exhibit 35** (staff should educate patients on infection control, hygiene, and related issues, along with strategies to address increased anxiety and stress resulting from the pandemic); CDC, *People with Developmental and Behavioral Disabilities* (May 27, 2020), attached to Bien Decl. as **Exhibit 36** (noting that individuals with developmental and behavioral disorders should take extra care of their mental health and it is critical that they take affirmative steps to identify and manage stress during the pandemic). The recent experience at San Quentin of numbers of incarcerated persons

refusing testing or refusing monitoring and treatment is evidence of the need for enhanced resources and attention necessary for patient education. In an atmosphere of fear, anxiety and distrust, communications tailored to the specific needs of the *Coleman* class and other incarcerated persons with cognitive differences are critical.

COVID-19 mitigation and prevention techniques, and strategies to address the additional stress imposed by the pandemic, should be incorporated into treatment plans. *See* Benjamin G. Druss, *Addressing the COVID-19 Pandemic in Populations with Serious Mental Illness* (Apr. 3, 2020), attached to Bien Decl. as **Exhibit 7** ("For any given patient, psychological symptoms will emerge in a unique personal and social context that should be considered in developing a treatment plan."); Ann K. Shinn, et al., *Perspectives on the COVID-19 Pandemic and Individuals with Serious Mental Illness*, Journal of Clinical Psychiatry (Apr. 28, 2020), attached to Bien Decl. as **Exhibit 31** (mental health providers must undertake individualized approaches tailored to individuals' weaknesses and strengths to help patients cope during the pandemic). Helping patients understand how they can be proactive in preventing infection will not only reduce stress and anxiety, but will also help reduce actual infection rates (both because of the preventive measures as such and because the reduction in stress and anxiety will likely have a positive impact on class members' overall health and immunity).

Access to clinicians via tele-mental health should be increased. For example, with COVID-19 at play, patients and/or clinicians may prefer a tele-mental health session to an in-person session. Both should be able to request this type of contact (as is true outside prisons). This can reduce COVID-19 risk not only to the patient and the clinician but also to custody staff, while also ensuring the patient receives meaningful, substantive treatment.

As this Court is aware, significant numbers of class members and other incarcerated persons in CDCR today are in cells or other housing without access to television, radio, tablets or any other entertainment devices. Some of these locations are the tent or gym housing set up for the pandemic. Other such housing includes reception centers and segregation units, as well as certain CTC and MHCB units. Access to reading, writing,

and drawing materials, activity packets, envelopes, and stamps is also limited. Immediate and thorough efforts must be taken to address these dangerous deprivations of basic and simple tools necessary to address the increased social anxiety, isolation, and seclusion caused by the pandemic and the near total lockdown and deprivation of programming and activities and treatment that has resulted.

Defendants should also use all available resources (including the Governor's emergency powers) to find ways to increase treatment, programming, and activities for the *Coleman* class and all incarcerated persons to combat the stress and isolation caused by COVID-19. Emergency powers could be used to procure entertainment devices, activity books, and other materials more quickly than through the usual processes. *See* AMEND: Changing Correctional Culture, *Urgent Memo, COVID-19 Outbreak: San Quentin Prison* (June 15, 2020), at 7, attached to Bien Decl. as **Exhibit 32** (individuals in medical isolation must be provided, at a minimum, free access to personal tablets with movies, increased access to free canteen items, personal effects and free phone calls, perhaps on state-owned cell phones, and daily opportunities for yard time."). Emergency powers can be used as necessary to resolve or remove technological and security barriers to procuring computers, tablets, radios, books, magazines and other supplies.

This urgent effort should start with the segregation units but must also include Reception Centers and other areas of the prisons that currently restrict access to entertainment devices due to lack of access to functioning electrical outlets or cable. The first section of Appendix A incorporated into Title 15, the Authorized Personal Property Schedule, is called Granted Exemption Requests. *See* Inmate Property: Matrix – Authorized Personal Property Schedule (Apr. 1, 2014), excerpt attached to Bien Decl. as **Exhibit 28**. The exemptions seem to identify all of the units in all of the prisons that do not allow entertainment devices for various reasons. *See id.* These portions of the regulations must be amended on an emergency basis to allow full access to entertainment devices. The alternative is serious mental health decompensation among class members and non-class members alike.

Defendants must take immediate steps to mitigate the harm caused to class members and all incarcerated persons by the total restrictions on visiting, volunteer-based programming, and activities (religious, educational, substance abuse, veteran, restorative justice, etc.). Free telephone calls must be expanded and made available to all prisoners, including those in quarantine. Visiting must be restored by setting up appropriate protocols for video visits, visits through glass, or other measures. Programming such as religious services, education, veterans' groups, AA groups, and others must be safely restored with appropriate limitations to assure social distancing and/or with increased use of technology.

Severe restrictions on yard time must be lifted—fresh air and exercise are crucial to stress reduction, and physical and mental health. Efforts to maximize fresh air and exercise, consistent with social distancing and other infection control measures, must be implemented.

Plaintiffs continue to urge Defendants to consider the distribution of cell phones (with appropriate security measures) to allow for communication with both family and mental health clinicians while maintaining social distancing. *See* AMEND: Changing Correctional Culture, *Urgent Memo, COVID-19 Outbreak: San Quentin Prison* (June 15, 2020), at 7, attached to Bien Decl. as **Exhibit 32**. Cell phones are already widely available (but contraband) in the prisons. Cell phones with appropriate security restrictions can be obtained and used without undue security risks.

Defendants must also, of course, continue to consider safe population reduction and density-decreasing measures. *See* AMEND: Changing Correctional Culture, *The Ethical Use of Medical Isolation – Not Solitary Confinement – to Reduce COVID-19 Transmission in Correctional Settings*, attached to Bien Decl. as **Exhibit 33** ("Prisons, jails, and other places of detention that are not able to comply with ethical standards of quarantine and medical isolation in the COVID-19 pandemic should urgently implement strategies to release or transfer people to locations that have the capacity to meet community standards of medical care."). Population reduction focusing on high-risk, vulnerable populations,

including the *Coleman* population, for targeted releases—rather than general releases based on political risk—must begin as soon as possible.

CONCLUSION

Plaintiffs appreciate the opportunity to provide the foregoing materials to the Court. Plaintiffs anticipate further focused discussions in the task force regarding what, if any, targeted efforts Defendants will commit to taking to address the serious risk of COVID-19 to the *Coleman* class, and to implement interventions to address the many significant mental health impacts of the pandemic. Plaintiffs expect to apprise the Court of the parties' progress on these issues in the forthcoming status conference statement on COVID-19 issues, and to continue to urge Defendants to take necessary steps to protect and treat the *Coleman* class.

CERTIFICATION

In preparing this brief, Plaintiffs' counsel reviewed the following Court orders: Minute Order, ECF No. 6741 (June 26, 2020); Order, ECF No. 6600 (Apr. 10, 2020).

DATED: July 2, 2020

Respectfully submitted,

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UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF CALIFORNIA

RALPH COLEMAN, et al.,

Plaintiffs,

v.

GAVIN NEWSOM, et al.,

Defendants.

Case No. 2:90-CV-00520-KJM-DB

DECLARATION OF MICHAEL W. BIEN IN SUPPORT OF PLAINTIFFS' BRIEF RE: EVIDENCE SUPPORTING SERIOUS MENTAL ILLNESS AS RISK FACTOR FOR COVID-19 AND NEED FOR ADDITIONAL MENTAL HEALTH INTERVENTIONS

Judge: Hon. Kimberly J. Mueller
Crtrm.: 3, 15th Floor, Sacramento

I, Michael W. Bien, declare:

1. I am an attorney duly admitted to practice before this Court. I am a partner in the law firm of Rosen Bien Galvan & Grunfeld LLP, counsel of record for Plaintiffs. I have personal knowledge of the facts set forth herein, and if called as a witness, I could competently so testify. I make this declaration in support of Plaintiffs' Brief Re Evidence Supporting Serious Mental Illness as Risk Factor for COVID-19 and Need for Additional Mental Health Interventions.

2. My office accessed the California Correctional Health Care Services (CCHCS) COVID-19 Monitoring Patient Registry on Wednesday, July 1 at approximately 8:36 a.m. The Registry is a log of CDCR incarcerated patients who have tested positive for COVID-19. The Registry includes patients whose COVID-19 cases are deemed resolved, but it excludes patients who are deceased or who have been released from custody. My office also accessed a version of the Registry filtered to show all patients who are "Out to Hospital." A redacted excerpt of a sample of the unfiltered version of the Registry is attached hereto as **Exhibit 1**. Given that the Registry is now hundreds of pages long and also contains patient information that would require redaction, I have attached only a redacted excerpt here. I am prepared to file or lodge *in camera* a full copy of the filtered and unfiltered versions of the Registry at the Court's request. The Registry can be downloaded in multiple formats including PDF and Excel.

3. The Registry showed 4,808 incarcerated patients including 1,275 *Coleman* class members. The filtered Registry showed 62 patients who were hospitalized. I calculated the average mean age of the hospitalized patients was 61.3 and the median age was 61.5. The range was from 84 to 32. Of the hospitalized patients, 40% were *Coleman* class members (25/62), six EOP and 19 CCCMS; 44% were *Armstrong* class members (27/62), and 21% were listed in the "DDP" disability column (13/62) (including members of the *Clark* class in the Developmental Disability Program, *Armstrong* Learning Disability, TABE score or reading level under grade 4). Many of the patients are members of more than one group (medical high risk, *Coleman*, *Armstrong*, *Clark*). Only 3% of the

hospitalized patients (2/62) were not identified as 55 or older, a *Coleman*, *Armstrong* or *Clark* class member or high risk medical.

4. We are provided with the identity of each CDCR incarcerated person who dies as a result of COVID-19. My office tracks and analyzes that data using information from medical and CDCR records. As of 3:00 p.m. on June 29, CDCR informed us of 22 deaths from COVID-19: 16 were from CIM, three from Avenal, two from CVSP and one from CIW. The average mean age of the patients who died was 62.6 and the median was 63. The range was from 83 to 41. Of the patients who died, 41% were *Coleman* class members participating in the Mental Health Services Delivery System (MHSDS) at the time of their deaths (9/22), and two additional patients had recent MHSDS histories evident in their medical records, 50% were *Armstrong* class members (11/22) and 18% were in the Developmental Disability Program (4/22) (*Clark* class or *Armstrong* Learning Disability, TABE score, reading level, under grade 4). Many of the patients who died were members of more than one group (medical high risk, *Coleman*, *Armstrong*, *Clark*). All of the patients who died (22/22) were either 55 or older, a *Coleman*, *Armstrong*, or *Clark* class member, or high risk medical. For 20 of the 22 deaths, we have information about race and ethnicity: 75% were people of color (9-Hispanic, 3-Black, 2-Asian/Pacific Islander and 1-American Indian/Alaskan Native). I am informed that one additional recently deceased class member, whose cause of death CDCR has not yet confirmed, tested positive for COVID-19 after his death. This person was 71 years old, a *Coleman* and *Armstrong* class member participant in the MHSDS at the CCCMS level of care, and incarcerated at San Quentin State Prison's Death Row.

5. Attached hereto as **Exhibit 2** is a true and correct copy of a study by the Centers for Disease Control and Prevention ("CDC"), dated June 15, 2020, entitled "Morbidity and Mortality Weekly Report: Coronavirus Disease 2019 Case Surveillance – United States, January 22-May 30, 2020, Vol. 69," available at https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6924e2-H.pdf. This recently published CDC study analyzes all reported cases of COVID-19 in the United States from

January 22 through May 30, 2020—1,320,488 lab confirmed cases—and measures demographic characteristics, underlying medical conditions and outcomes.

6. The CDC study found solid confirmation that underlying conditions, including psychological/psychiatric conditions, are the most important predictor of adverse outcomes from infection with COVID-19. Hospitalizations were six times higher among patients with a reported underlying condition (45.4%) than those without (7.6%). Deaths were 12 times higher among patients with reported underlying conditions (19.5%) compared to those without underlying conditions (1.6%). The percentage of ICU admissions among persons with underlying conditions age 60-69 was 11%, and for those age 70-79 was 12%. The death rate for persons age 80 and over with at least one underlying condition was 50% (compared to 30% for those 80 and older without an underlying condition).

7. For purposes of the study, CDC defined "underlying health conditions" as diabetes, cardiovascular disease, severe obesity, chronic renal, liver or lung disease, immuno-compromised condition, autoimmune condition and neurologic condition including neurodevelopmental, intellectual, physical, visual, or hearing impairment, or psychological/psychiatric condition, or other medical condition. *See* **Exhibit 2** at 762, tbl 2 & n.*. That is, people with psychiatric, developmental, and physical disabilities as well as people who are deaf, hard of hearing, or blind, are also at high risk for adverse outcomes from COVID-19.

8. Advanced age is even more of a risk factor than previously known: According to the CDC study, older adults are far more likely to contract COVID-19 than average and are also far more likely to be hospitalized and die. While the overall incidence of infection was 403 cases per 100,000 (median age 48), the per-100,000 incidence for children under nine was 51, the incidence for people ages 70-79 was 464, and the incidence for people age 80 and older was 902. Overall, 14% of patients were hospitalized, 2% admitted to ICU and 5% died, while 28% of the patients who were 80 and over died.

9. Distinctions by race and ethnicity continue to be extremely significant: According to the CDC study, of all COVID-19 cases with known race and ethnicity 33% were Hispanic, 22% were Black, and 1.3% were Native American while these groups respectively account for 18%, 13%, and 0.7% of the overall population in the United States. The racial disparities in all aspects of our society are sharply visible in the pandemic.

10. On June 19, 2020, in response to the Court's questions and Dr. Joseph Bick's assertions at the June 12, 2020 status conference, Plaintiffs sent a letter to Defendants and the Special Master gathering resources including scientific research and public health guidance demonstrating a strong link between serious mental illness and COVID-19. The letter also explained, in light of the novelty of the pandemic, the need for CDCR's COVID-19 response to rely in part on research and guidance regarding analogous medical or behavioral conditions, and common sense. On June 23, 2020, during the Twenty-Third COVID-19 Taskforce meeting led by the Special Master, the parties briefly discussed the issues raised in Plaintiffs' letter. At the June 26, 2020 status conference in this matter, Plaintiffs informed the Court of these materials and Defendants confirmed that addressing the materials required additional discussions and work.

11. Attached hereto as **Exhibit 3** is a true and correct copy of guidance from the Department of Health & Human Services, Centers for Medicare and Medicaid Services, dated March 30, 2020, entitled "Guidance for Infection Control and Prevention of Coronavirus Disease (COVID-19) in Hospitals, Psychiatric Hospitals, and Critical Access Hospitals (CAHs): FAQs, Considerations for Patient Triage, Placement, Limits to Visitation and Availability of 1135 waivers," available at https://www.cms.gov/files/document/qso-20-13-hospitals-cahs-revised.pdf.

12. Attached hereto as **Exhibit 4** is a true and correct copy of guidance from the Department of Health & Human Services, Centers for Medicare and Medicaid Services, dated March 30, 2020, entitled "Guidance for Infection Control and Prevention of Coronavirus Disease 2019 (COVID-19) in Intermediate Care Facilities for Individuals with

Intellectual Disabilities (ICF/IIDs) and Psychiatric Residential Treatment Facilities (PRTFs)," available at https://www.cms.gov/files/document/qso-20-23-icf-iid-prtf.pdf.

13. Attached hereto as **Exhibit 5** is a true and correct copy of guidance from the CDC, dated April 7, 2020, entitled "Coronavirus Disease 2019 (COVID-19): People with Disabilities," available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-disabilities.html.

14. Attached hereto as **Exhibit 6** is a true and correct copy of an article by Julia Reis, published by *Healthline*, dated April 7, 2020, entitled "COVID-19 Can Have Serious Effects on People with Mental Health Disorders," available at https://www.healthline.com/health-news/covid-19-serious-effects-people-with-mental-health-disorders.

15. Attached hereto as **Exhibit 7** is a true and correct copy of an article by Benjamin G. Druss, published by *JAMA Psychiatry*, dated April 3, 2020, entitled "Addressing the COVID-19 Pandemic in Populations With Serious Mental Illness," available at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2764227.

16. Attached hereto as **Exhibit 8** is a true and correct copy of an article by Nicole M. Benson, et al., published by *The Lancet*, dated May 11, 2020, entitled "COVID-19 Testing and Patients in Mental Health Facilities," available at https://www.thelancet.com/action/showPdf?pii=S2215-0366%2820%2930198-X.

17. Attached hereto as **Exhibit 9** is a true and correct copy of an article by Andrea Fiorillo, et al., published by *Psychiatric Times*, dated May 15, 2020, entitled "Psychosocial Interventions to Reduce Premature Mortality in Patients With Serious Mental Illness," available at https://www.psychiatrictimes.com/special-reports/psychosocial-interventions-reduce-premature-mortality-patients-serious-mental-illness.

18. Attached hereto as **Exhibit 10** is a true and correct copy of an article by Joseph Shapiro, published by NPR, dated June 9, 2020, entitled "COVID-19 Infections And Deaths Are Higher Among Those With Intellectual Disabilities," available at

https://www.npr.org/2020/06/09/872401607/covid-19-infections-and-deaths-are-higher-among-those-with-intellectual-disabili.

19. Attached hereto as **Exhibit 11** is a true and correct copy of an article by Marla Milling, published by *Forbes*, dated May 28, 2020, entitled "People with Intellectual and Developmental Disabilities More Likely to Die from COVID-19," available at https://www.forbes.com/sites/marlamilling/2020/05/28/people-with-intellectual-and-developmental-disabilities-more-likely-to-die-from-covid-19/#87a10bb33159.

20. Attached hereto as **Exhibit 12** is a true and correct copy of an information sheet from the Alzheimer's Association, accessed on June 29, 2020, entitled "Coronavirus (COVID-19): Tips for Dementia Caregivers," available at https://www.dhcs.ca.gov/Documents/COVID-19/Alzheimers-Association-Guidance-on-COVID-19.pdf.

21. Attached hereto as **Exhibit 13** is a true and correct copy of guidance from the World Health Organization ("WHO"), dated 2018, entitled "Management of Physical Health Conditions in Adults with Severe Mental Disorders," available at https://apps.who.int/iris/bitstream/handle/10665/275718/9789241550383-eng.pdf.

22. Attached hereto as **Exhibit 14** is a true and correct copy of an article by Matthew J. Akiyama, et al., published by *New England Journal of Medicine,* dated May 28, 2020, entitled "Flattening the Curve for Incarcerated Populations – COVID 19 in Jails and Prisons," available at https://www.nejm.org/doi/10.1056/NEJMp2005687.

23. Attached hereto as **Exhibit 15** is a true and correct excerpted copy of a letter from over 3,000 medical professionals to the U.S. Immigration and Customs Enforcement (ICE) agency, dated March 13, 2020, entitled "Open Letter to ICE from Medical Professionals Regarding COVID-19," available at https://nylpi.org/wp-content/uploads/2020/03/FINAL-LETTER-Open-Letter-to-ICE-From-Medical-Professionals-Regarding-COVID-19.pdf. Due to the lengthy list of over 3,000 medical professional signatories—spanning 66 pages—I have excerpted the letter to include only the first page of signatories. The full list is available at the above link.

24. Attached hereto as **Exhibit 16** is a true and correct copy of an article by Laura M. Maruschak, et al., published by the *American Journal of Public Health*, dated October 2009, entitled "Pandemic Influenza and Jail Facilities and Populations," available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504367/.

25. Attached hereto as **Exhibit 17** is a true and correct copy of an article by Catherine Kariuki-Nyuthea, et al., published in *Comorbidity of Mental and Physical Disorders*, dated 2015 (print version), entitled "Anxiety and Related Disorders and Physical Illness" available at https://www.karger.com/Article/Pdf/365538.

26. Attached hereto as **Exhibit 18** is a true and correct copy of an article by Joshua D. Rosenblat, et al., published in *Brain Sciences*, dated October 30, 2017, entitled "Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications," available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5704151/pdf/brainsci-07-00144.pdf.

27. Attached hereto as **Exhibit 19** is a true and correct copy of an article by Janice K. Kiecolt-Glasera, et al., published in the *Journal of Psychosomatic Research*, dated 2002, entitled "Depression and immune function: Central pathways to morbidity and mortality," available at http://pni.osumc.edu/KG%20Publications%20(pdf)/154.pdf.

28. Attached hereto as **Exhibit 20** is a true and correct copy of an article by the American Psychological Association, dated February 23, 2006, entitled "Stress Weakens the Immune System," available at https://www.apa.org/research/action/immune.

29. Attached hereto as **Exhibit 21** is a true and correct copy of the Author Manuscript version of an article by Gretchen N. Neigh, et al., published in the *Current Opinion in Pharmacology*, dated August 2016, entitled "Co-Morbidity of PTSD and Immune System Dysfunction: Opportunities for Treatment," available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4992603/pdf/nihms805030.pdf.

30. Attached hereto as **Exhibit 22** is a true and correct copy of an article by Sukanta Saha, et al., published in *Archives of General Psychiatry*, dated 2007, entitled "A Systematic Review of Mortality in Schizophrenia, Is the Differential Mortality Gap

Worsening Over Time," available at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/210034.

31. Attached hereto as **Exhibit 23** is a true and correct copy of an article by Keramet Reiter, et al., published in the *American Journal of Public Health*, dated January 1, 2020, entitled "Psychological Distress in Solitary Confinement: Symptoms, Severity, and Prevalence in the United States, 2017–2018," available at https://ajph.aphapublications.org/doi/10.2105/AJPH.2019.305375.

32. Attached hereto as **Exhibit 24** is a true and correct copy of an article by Jeffrey L. Metzner, et al., published in the *Journal of the American Academy of Psychiatry and the Law*, dated 2010, entitled "Solitary Confinement and Mental Illness in U.S. Prisons: A Challenge for Medical Ethics," available at http://jaapl.org/content/jaapl/38/1/104.full.pdf.

33. Attached hereto as **Exhibit 25** is a true and correct copy of the Brief of Amici Curiae Professors and Practitioners of Psychiatry and Psychology in Support of Petitioner, *Prieto v. Clarke*, No. 15-31, 2015 WL 4720278 (U.S. Aug. 5, 2015), available at https://www.scotusblog.com/wp-content/uploads/2015/10/PrietoClarke_AmicusMentalHealthExperts.pdf.

34. Attached hereto as **Exhibit 26** is a true and correct copy of an article by Craig Haney, published in *Crime and Justice*, dated March 9, 2018, entitled "The Psychological Effects of Solitary Confinement: A Systematic Critique" available at https://www.researchgate.net/publication/323674531_The_Psychological_Effects_of_Solitary_Confinement_A_Systematic_Critique.

35. Attached hereto as **Exhibit 27** is a true and correct copy of an article by Stuart Grassian, published in the *Washington University Journal of Law & Policy*, dated 2006, entitled "Psychiatric Effects of Solitary Confinement," available at https://openscholarship.wustl.edu/cgi/viewcontent.cgi?article=1362&context=law_journal_law_policy.

36. Attached hereto as **Exhibit 28** is a true and correct copy of an excerpt of relevant pages from the California Code of Regulations Title 15 Inmate Property; Matrix – Authorized Personal Property Schedule, last revised April 1, 2014, available at https://www.cdcr.ca.gov/regulations/wp-content/uploads/sites/171/2019/08/APPS-Rev-4-1-14.pdf?label=Authorized%20Personal%20Property%20Schedule%20(APPS)%20(Rev.%204/1/14)&from=https://www.cdcr.ca.gov/regulations/cdcr-regulations/dom-appendices/.

37. Attached hereto as **Exhibit 29** is a true and correct copy of the Declaration of Robert M. Sapolsky filed in *Arevalo v. Decker*, No. 1:20-cv-02982, Dkt. 3-3 (S.D.N.Y. Apr. 13, 2020), available at https://federaldefendersny.org/pdfs/2020.05.11%20CLE/Abrego%20v.%20Decker%20-%20Sapolsky%20Decl.%20and%20CV%20(1)_Redacted%5B1%5D.pdf (redactions in original).

38. Attached hereto as **Exhibit 30** is a true and correct copy of an article by Jeffrey L. Geller, et al., published by the American Psychiatric Association, *Psychiatric News*, dated April 7, 2020, entitled "Patients With SMI in the Age of COVID-19: What Psychiatrists Need to Know" available at https://doi.org/10.1176/appi.pn.2020.4b39.

39. Attached hereto as **Exhibit 31** is a true and correct copy of an article by Ann K. Shinn, et al., published by the *Journal of Clinical Psychiatry*, dated 2020, last accessed June 30, 2020, entitled "Perspectives on the COVID-19 Pandemic and Individuals With Serious Mental Illness," available at https://www.psychiatrist.com/JCP/article/Pages/2020/v81/20com13412.aspx.

40. Attached hereto as **Exhibit 32** is a true and correct copy of a memorandum by AMEND: Changing Correctional Culture, dated June 15, 2020, entitled "Urgent Memo: COVID-19 Outbreak: San Quentin State Prison," available at https://amend.us/wp-content/uploads/2020/06/COVID19-Outbreak-SQ-Prison-6.15.2020.pdf.

41. Attached hereto as **Exhibit 33** is a true and correct copy of a memorandum by David Cloud, et al., published by AMEND: Changing Correctional Culture, dated April

9, 2020, entitled "The Ethical Use of Medical Isolation – Not Solitary Confinement – to Reduce COVID-19 Transmission in Correctional Settings," available at https://amend.us/wp-content/uploads/2020/04/Medical-Isolation-vs-Solitary_Amend.pdf.

42. Attached hereto as **Exhibit 34** is a true and correct copy of an article by Aravinthan Varatharaj, et al., entitled Neurological and Neuropsychiatric Complications of COVID-19 in 153 Patients: A UK-Wide Surveillance Study, published in *The Lancet*, dated June 25, 2020, available at https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30287-X/fulltext.

43. Attached hereto as **Exhibit 35** is a true and correct copy of guidance from the CDC dated June 25, 2020, entitled "Preparing for COVID-19 in Nursing Homes," available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/long-term-care.html.

44. Attached hereto as **Exhibit 36** is a true and correct copy of guidance from the CDC dated May 27, 2020, entitled "People with Developmental and Behavioral Disabilities," available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-developmental-behavioral-disabilities.html.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration is executed at San Francisco, California this 2d day of July, 2020.

/s/ Michael W. Bien
Michael W. Bien

EXHIBIT 1

COVID MONITORING

Registry Definition

Statewide or Multiple Institutions

Identification & Housing									COVID Status			
Current Institution	First Testing Institution	CDCR#	Last Name	Age	Care Team	Housing Facility	Cell Bed	MHLOC	COVID Status	COVID Risk Factor Count	COVID Weighted Risk Score	First Positive Test
CRC	CRC	[redacted]	[redacted]	38	Facility D1	CRC-D	[redacted]	CCCMS	Confirmed Active	0	0	6/29/2020
CRC	CRC	[redacted]	[redacted]	46	Facility D1	CRC-D	[redacted]		Confirmed Active	0	0	6/29/2020
CRC	CRC	[redacted]	[redacted]	52	Facility D2	CRC-D	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	44	WB 1	SQ-A	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	43	WB 2	SQ-A	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	59	NSEG	SQ-A	[redacted]		Confirmed Active	1	1	6/29/2020
SQ	SQ	[redacted]	[redacted]	54	NSEG	SQ-A	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	58	WB 1	SQ-A	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	48	WB 1	SQ-A	[redacted]	CCCMS	Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	56	WB 2	SQ-A	[redacted]		Confirmed Active	1	1	6/29/2020
SQ	SQ	[redacted]	[redacted]	61	WB 1	SQ-A	[redacted]		Confirmed Active	1	1	6/29/2020
SQ	SQ	[redacted]	[redacted]	70	NSEG	SQ-A	[redacted]		Confirmed Active	1	4	6/29/2020

Institution(s): Multiple
Care Team(s): All
Housing/Facility: All

Report run: 7/1/2020 8:36:06 AM

COVID MONITORING

Registry Definition

Statewide or Multiple Institutions

Disability	
DDP	DPP
TABE < 4.0	
TABE < 4.0	

Institution(s): Multiple
Care Team(s): All
Housing/Facility: All

Report run: 7/1/2020 8:36:06 AM

EXHIBIT 2

Morbidity and Mortality Weekly Report

Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020

Erin K. Stokes, MPH[1,*]; Laura D. Zambrano, PhD[1,*]; Kayla N. Anderson, PhD[1]; Ellyn P. Marder, DrPH[1]; Kala M. Raz, MPH[1]; Suad El Burai Felix, MPH[1]; Yunfeng Tie, PhD[1]; Kathleen E. Fullerton, MPH[1]

On June 15, 2020, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

The coronavirus disease 2019 (COVID-19) pandemic resulted in 5,817,385 reported cases and 362,705 deaths worldwide through May, 30, 2020,† including 1,761,503 aggregated reported cases and 103,700 deaths in the United States.§ Previous analyses during February–early April 2020 indicated that age ≥65 years and underlying health conditions were associated with a higher risk for severe outcomes, which were less common among children aged <18 years (*1–3*). This report describes demographic characteristics, underlying health conditions, symptoms, and outcomes among 1,320,488 laboratory-confirmed COVID-19 cases individually reported to CDC during January 22–May 30, 2020. Cumulative incidence, 403.6 cases per 100,000 persons,¶ was similar among males (401.1) and females (406.0) and highest among persons aged ≥80 years (902.0). Among 599,636 (45%) cases with known information, 33% of persons were Hispanic or Latino of any race (Hispanic), 22% were non-Hispanic black (black), and 1.3% were non-Hispanic American Indian or Alaska Native (AI/AN). Among 287,320 (22%) cases with sufficient data on underlying health conditions, the most common were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Overall, 184,673 (14%) patients were hospitalized, 29,837 (2%) were admitted to an intensive care unit (ICU), and 71,116 (5%) died. Hospitalizations were six times higher among patients with a reported underlying condition (45.4%) than those without reported underlying conditions (7.6%). Deaths were 12 times higher among patients with reported underlying conditions (19.5%) compared with those without reported underlying conditions (1.6%). The COVID-19 pandemic continues to be severe, particularly in certain population groups. These preliminary findings underscore the need to build on current efforts to collect and analyze case data, especially among those with underlying health conditions. These data are used to monitor trends in COVID-19 illness, identify and respond to localized incidence increase, and inform policies and practices designed to reduce transmission in the United States.

State and territorial health departments report daily aggregate counts of COVID-19 cases and deaths to CDC; these were tabulated according to date of report to examine reporting trends during January 22–May 30. In addition to aggregate counts, individual COVID-19 case reports were submitted via a CDC COVID-19 case report form** and the National Notifiable Diseases Surveillance System (NNDSS).†† Jurisdictions voluntarily report confirmed and probable§§ cases from reports submitted by health care providers and laboratories. A laboratory-confirmed COVID-19 case was defined as a person with a positive test result for SARS-CoV-2, the virus that causes COVID-19, from a respiratory specimen, using real-time reverse transcription–polymerase chain reaction testing. COVID-19 case data reported from 50 states, New York City, and the District of Columbia¶¶ were analyzed to examine reported demographic characteristics, underlying health conditions, clinical signs and symptoms, and severe outcomes, including hospitalization, ICU admission, and death. Data were missing for age, sex, and race or ethnicity in

*These authors contributed equally to this report.

† https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

§ CDC official counts of cases and deaths, released daily on https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html, are aggregate counts from reporting jurisdictions. Throughout the COVID-19 pandemic, CDC has been tracking both aggregate and individual (i.e., line-list) counts of cases and deaths. For aggregate counts, from January 22 to March 2, 2020, CDC provided laboratory confirmation for all U.S. confirmed cases. Starting March 3, jurisdiction partners validated aggregate counts each night for report out at 12 p.m. the following day by CDC. For individual counts, jurisdiction partners electronically submit standardized information for individual cases of COVID-19 to CDC. From April 14, aggregate and individual counts included confirmed and probable cases and deaths, according to the Council of State and Territorial Epidemiologists position statement Interim 20-ID-01 (https://cdn.ymaws.com/www.cste.org/resource/resmgr/2020ps/interim-20-id-01_covid-19.pdf; https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/).

¶ Incidence was calculated per 100,000 population using 2018 U.S. Census population estimates for U.S. states and the District of Columbia obtained from CDC WONDER (https://wonder.cdc.gov/single-race-population.html).

** https://www.cdc.gov/coronavirus/2019-ncov/php/reporting-pui.html.

†† https://wwwn.cdc.gov/nndss; https://wwwn.cdc.gov/nndss/covid-19-response.html.

§§ According to the Council of State and Territorial Epidemiologists position statement Interim 20-ID-01, a probable case must 1) meet clinical criteria and epidemiologic criteria with no confirmatory laboratory testing performed; 2) have presumptive laboratory evidence, including detection of specific antigen or antibody in a clinical specimen, and meet clinical criteria or epidemiologic criteria; or 3) meet vital records criteria with no confirmatory laboratory testing performed. (https://cdn.ymaws.com/www.cste.org/resource/resmgr/2020ps/interim-20-id-01_covid-19.pdf)

¶¶ Cases reported from U.S. territories were not included in the analysis because of limited case reporting and lack of available demographically stratified census data. Cases excluded from this analysis include those reported from Guam (116), the Northern Mariana Islands (16), Puerto Rico (one), and the U.S. Virgin Islands (71).

<1%, 1%, and 55% of reports, respectively.*** Cases reported without sex or age data were excluded from this analysis as were cases meeting only the probable case definition, along with persons repatriated to the United States from Wuhan, China, or the Diamond Princess cruise ship. Cumulative incidence was estimated using 2018 population estimates. Because of the high prevalence of missing race and ethnicity data, estimates of incidence and proportions of underlying health conditions, symptoms, and severe outcomes by race and ethnicity were not described. Analyses are descriptive and statistical comparisons were not performed.

CDC received notification of the first case of laboratory-confirmed COVID-19 in the United States on January 22, 2020.††† As of May 30, an aggregate 1,761,503 U.S. COVID-19 cases and 103,700 deaths had been reported (Figure).§§§ The 7-day moving average number¶¶¶ of new daily cases peaked on April 12 (31,994) and deaths peaked on April 21 (2,856). As of May 30, the 7-day moving average numbers of new cases were 19,913 per day and deaths were 950 per day.

Among the 1,761,503 aggregate cases reported to CDC during January 22–May 30, individual case reports for 1,406,098 were submitted to CDC case surveillance. After exclusions, data for 1,320,488 (94%) cases were analyzed. Median age was 48 years (interquartile range = 33–63 years). Incidence was 403.6 cases per 100,000 population (Table 1) and was similar among females (406.0) and males (401.1).**** Incidence was higher among persons aged 40–49 years (541.6) and 50–59 years (550.5) than among those aged 60–69 years (478.4) and 70–79 years (464.2). Incidence was highest among persons aged ≥80 years (902.0)†††† and lowest among children aged ≤9 years (51.1). Among the 599,636 (45%) cases with information on both race and ethnicity, 36% of persons were non-Hispanic white, 33% were Hispanic, 22% were black, 4% were non-Hispanic Asian, 4% were non-Hispanic, other or multiple race, 1.3% were AI/AN, and <1% were non-Hispanic Native Hawaiian or other Pacific Islander.

Symptom status (symptomatic versus asymptomatic) was reported for 616,541 (47%) cases; among these, 22,007 (4%) were asymptomatic. Among 373,883 (28%) cases with data on individual symptoms, 70% noted fever, cough, or shortness of breath; 36% reported muscle aches, and 34% reported headache (Table 2). Overall, 31,191 (8%) persons reported loss of smell or taste.§§§§ Among patients aged ≥80 years, 60% reported fever, cough, or shortness of breath. No other symptoms were reported by >10% of persons in this age group.

Among 287,320 (22%) cases with data on individual underlying health conditions, those most frequently reported were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%) (Table 2); the reported proportions were similar among males and females. The frequency of conditions reported varied by age group: cardiovascular disease was uncommon among those aged ≤39 years but was reported in approximately half of the cases among persons aged ≥70 years. Among 63,896 females aged 15–44 years with known pregnancy status, 6,708 (11%) were reported to be pregnant.

Among the 1,320,488 cases, outcomes for hospitalization, ICU admission, and death were available for 46%, 14%, and 36%, respectively. Overall, 184,673 (14%) patients were hospitalized, including 29,837 (2%) admitted to the ICU; 71,116 (5%) patients died (Table 3). Severe outcomes were more commonly reported for patients with reported underlying conditions. Hospitalizations were six times higher among patients with a reported underlying condition than those without reported underlying conditions (45.4% versus 7.6%). Deaths were 12 times higher among patients with reported underlying conditions compared with those without reported underlying conditions (19.5% versus 1.6%). The percentages of males who were hospitalized (16%), admitted to the ICU (3%), and who died (6%) were higher than were those for females (12%, 2%, and 5%, respectively). The percentage of ICU admissions was highest among persons with reported underlying conditions aged 60–69 years (11%) and 70–79 years (12%). Death was most commonly reported among persons aged ≥80 years regardless of the presence of underlying conditions (with underlying conditions 50%; without 30%).

Discussion

As of May 30, a total of 1,761,503 aggregate U.S. cases of COVID-19 and 103,700 associated deaths were reported to CDC. Although average daily reported cases and deaths are declining, 7-day moving averages of daily incidence of COVID-19 cases indicate ongoing community transmission.¶¶¶¶

*** Cases reported as Hispanic were categorized as "Hispanic or Latino persons of any race" regardless of availability of race data.

††† The first laboratory-confirmed case of COVID-19 in the United States was confirmed on January 20, 2020, and reported to CDC on January 22, 2020. The upper quartile of the lag between onset date and reporting to CDC was 15 days.

§§§ From April 15 to May 30, 2020, these aggregate counts include both confirmed and probable cases and deaths. Overall, <1% of cases and 3.1% of deaths were classified as probable.

¶¶¶ The 7-day moving average of new cases and deaths (current day + 6 preceding days / 7) was calculated to smooth expected variations in daily counts.

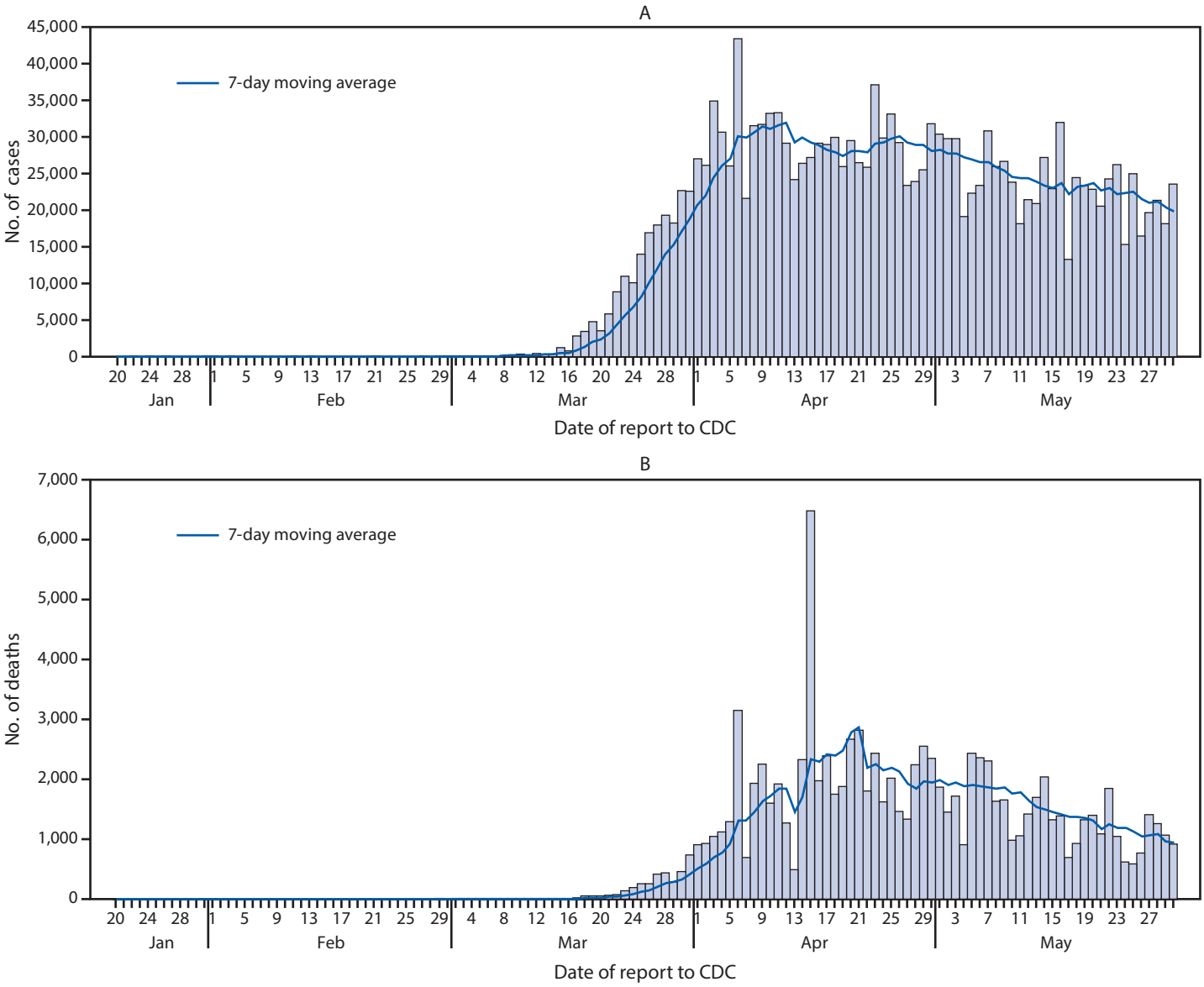
**** In some age groups, males had higher incidence, and in some age groups, females had higher incidence.

†††† Among those aged ≥85 years, incidence was 1,138 per 100,000.

§§§§ Responses include data from standardized fields supplemented with data from free-text fields; therefore, persons exhibiting this symptom might be underreported.

¶¶¶¶ Community transmission is defined by states and reflects varying conditions at the local and state levels.

FIGURE. Daily number of COVID-19 cases*,†,§,¶ (A) and COVID-19–associated deaths (B) reported to CDC — United States, January 22–May 30, 2020**



Abbreviation: COVID-19 = coronavirus disease 2019.

* From April 14, 2020, aggregate case counts reported by CDC included deaths attributable to both confirmed and probable COVID-19 as classified by reporting jurisdictions, using the Council of State and Territorial Epidemiologists position statement Interim-ID-20-01 (https://cdn.ymaws.com/www.cste.org/resource/resmgr/2020ps/interim-20-id-01_covid-19.pdf).

† The upper quartile of the lag between onset date and reporting to CDC was 15 days.

§ The daily number of deaths reported by jurisdictions on April 14 includes 4,141 deaths newly classified as probable.

¶ Overall <1% of cases reported in aggregate to CDC were classified as probable.

** Overall 3.1% of deaths reported in aggregate to CDC were classified as occuring in persons with probable cases.

The COVID-19 case data summarized here are essential statistics for the pandemic response and rely on information systems developed at the local, state, and federal level over decades for communicable disease surveillance that were rapidly adapted to meet an enormous, new public health threat. CDC aggregate counts are consistent with those presented through the Johns Hopkins University (JHU) Coronavirus Resource Center, which reported a cumulative total of 1,770,165 U.S. cases and 103,776 U.S. deaths on May 30, 2020.***** Differences in aggregate counts between CDC and

***** COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University is a publicly available data tracker that extracts data from state, territorial, and local public health websites (https://coronavirus.jhu.edu/us-map). Data are archived in GitHub (https://github.com/CSSEGISandData/COVID-19/blob/master/csse_covid_19_data/csse_covid_19_daily_reports_us/05-30-2020.csv).

TABLE 1. Reported laboratory-confirmed COVID-19 cases and estimated cumulative incidence,* by sex† and age group — United States, January 22–May 30, 2020

	Males		Females		Total	
Age group (yrs)	No. (%)	Cumulative incidence*	No. (%)	Cumulative incidence*	No. (%)	Cumulative incidence*
0–9	10,743 (1.7)	52.5	9,715 (1.4)	49.7	20,458 (1.5)	51.1
10–19	24,302 (3.8)	113.4	24,943 (3.7)	121.4	49,245 (3.7)	117.3
20–29	85,913 (13.3)	370.0	96,556 (14.3)	434.6	182,469 (13.8)	401.6
30–39	108,319 (16.8)	492.8	106,530 (15.8)	490.5	214,849 (16.3)	491.6
40–49	109,745 (17.0)	547.0	109,394 (16.2)	536.2	219,139 (16.6)	541.6
50–59	119,152 (18.4)	568.8	116,622 (17.3)	533.0	235,774 (17.9)	550.5
60–69	93,596 (14.5)	526.9	85,411 (12.7)	434.6	179,007 (13.6)	478.4
70–79	53,194 (8.2)	513.7	52,058 (7.7)	422.7	105,252 (8.0)	464.2
≥80	41,394 (6.4)	842.0	72,901 (10.8)	940.0	114,295 (8.7)	902.0
All ages	**646,358 (100.0)**	**401.1**	**674,130 (100.0)**	**406.0**	**1,320,488 (100.0)**	**403.6**

Abbreviation: COVID-19 = coronavirus disease 2019.
* Per 100,000 population.
† The analytic dataset excludes cases reported through case surveillance that were missing information on sex (n = 19,918) or age (n = 2,379).

TABLE 2. Reported underlying health conditions* and symptoms† among persons with laboratory-confirmed COVID-19, by sex and age group — United States, January 22–May 30, 2020

	No. (%)											
		Sex		Age group (yrs)								
Characteristic	Total	Male	Female	≤9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	≥80
Total population	**1,320,488**	**646,358**	**674,130**	**20,458**	**49,245**	**182,469**	**214,849**	**219,139**	**235,774**	**179,007**	**105,252**	**114,295**
Underlying health condition§												
Known underlying medical condition status*	**287,320 (21.8)**	138,887 (21.5)	148,433 (22.0)	2,896 (14.2)	7,123 (14.5)	27,436 (15.0)	33,483 (15.6)	40,572 (18.5)	54,717 (23.2)	50,125 (28.0)	34,400 (32.7)	36,568 (32.0)
Any cardiovascular disease¶	**92,546 (32.2)**	47,567 (34.2)	44,979 (30.3)	78 (2.7)	164 (2.3)	1,177 (4.3)	3,588 (10.7)	8,198 (20.2)	16,954 (31.0)	21,466 (42.8)	18,763 (54.5)	22,158 (60.6)
Any chronic lung disease	**50,148 (17.5)**	20,930 (15.1)	29,218 (19.7)	363 (12.5)	1,285 (18)	4,537 (16.5)	5,110 (15.3)	6,127 (15.1)	8,722 (15.9)	9,200 (18.4)	7,436 (21.6)	7,368 (20.1)
Renal disease	**21,908 (7.6)**	12,144 (8.7)	9,764 (6.6)	21 (0.7)	34 (0.5)	204 (0.7)	587 (1.8)	1,273 (3.1)	2,789 (5.1)	4,764 (9.5)	5,401 (15.7)	6,835 (18.7)
Diabetes	**86,737 (30.2)**	45,089 (32.5)	41,648 (28.1)	12 (0.4)	225 (3.2)	1,409 (5.1)	4,106 (12.3)	9,636 (23.8)	19,589 (35.8)	22,314 (44.5)	16,594 (48.2)	12,852 (35.1)
Liver disease	**3,953 (1.4)**	2,439 (1.8)	1,514 (1.0)	5 (0.2)	19 (0.3)	132 (0.5)	390 (1.2)	573 (1.4)	878 (1.6)	1,074 (2.1)	583 (1.7)	299 (0.8)
Immunocompromised	**15,265 (5.3)**	7,345 (5.3)	7,920 (5.3)	61 (2.1)	146 (2.0)	646 (2.4)	1,253 (3.7)	2,005 (4.9)	3,190 (5.8)	3,421 (6.8)	2,486 (7.2)	2,057 (5.6)
Neurologic/ Neurodevelopmental disability	**13,665 (4.8)**	6,193 (4.5)	7,472 (5.0)	41 (1.4)	113 (1.6)	395 (1.4)	533 (1.6)	734 (1.8)	1,338 (2.4)	2,006 (4.0)	2,759 (8.0)	5,746 (15.7)
Symptom§												
Known symptom status†	**373,883 (28.3)**	178,223 (27.6)	195,660 (29.0)	5,188 (25.4)	12,689 (25.8)	51,464 (28.2)	59,951 (27.9)	62,643 (28.6)	70,040 (29.7)	52,178 (29.1)	28,583 (27.2)	31,147 (27.3)
Fever, cough, or shortness of breath	**260,706 (69.7)**	125,768 (70.6)	134,938 (69.0)	3,278 (63.2)	7,584 (59.8)	35,072 (68.1)	42,016 (70.1)	45,361 (72.4)	51,283 (73.2)	37,701 (72.3)	19,583 (68.5)	18,828 (60.4)
Fever††	**161,071 (43.1)**	80,578 (45.2)	80,493 (41.1)	2,404 (46.3)	4,443 (35.0)	20,381 (39.6)	25,887 (43.2)	28,407 (45.3)	32,375 (46.2)	23,591 (45.2)	12,190 (42.6)	11,393 (36.6)
Cough	**187,953 (50.3)**	89,178 (50.0)	98,775 (50.5)	1,912 (36.9)	5,257 (41.4)	26,284 (51.1)	31,313 (52.2)	34,031 (54.3)	38,305 (54.7)	27,150 (52.0)	12,837 (44.9)	10,864 (34.9)
Shortness of breath	**106,387 (28.5)**	49,834 (28.0)	56,553 (28.9)	339 (6.5)	2,070 (16.3)	13,649 (26.5)	16,851 (28.1)	18,978 (30.3)	21,327 (30.4)	16,018 (30.7)	8,971 (31.4)	8,184 (26.3)
Myalgia	**135,026 (36.1)**	61,922 (34.7)	73,104 (37.4)	537 (10.4)	3,737 (29.5)	21,153 (41.1)	26,464 (44.1)	28,064 (44.8)	28,594 (40.8)	17,360 (33.3)	6,015 (21.0)	3,102 (10.0)
Runny nose	**22,710 (6.1)**	9,900 (5.6)	12,810 (6.5)	354 (6.8)	1,025 (8.1)	4,591 (8.9)	4,406 (7.3)	4,141 (6.6)	4,100 (5.9)	2,671 (5.1)	923 (3.2)	499 (1.6)
Sore throat	**74,840 (20.0)**	31,244 (17.5)	43,596 (22.3)	664 (12.8)	3,628 (28.6)	14,493 (28.2)	14,855 (24.8)	14,490 (23.1)	13,930 (19.9)	8,192 (15.7)	2,867 (10.0)	1,721 (5.5)
Headache	**128,560 (34.4)**	54,721 (30.7)	73,839 (37.7)	785 (15.1)	5,315 (41.9)	23,723 (46.1)	26,142 (43.6)	26,245 (41.9)	26,057 (37.2)	14,735 (28.2)	4,163 (14.6)	1,395 (4.5)
Nausea/Vomiting	**42,813 (11.5)**	16,549 (9.3)	26,264 (13.4)	506 (9.8)	1,314 (10.4)	6,648 (12.9)	7,661 (12.8)	8,091 (12.9)	8,737 (12.5)	5,953 (11.4)	2,380 (8.3)	1,523 (4.9)
Abdominal pain	**28,443 (7.6)**	11,553 (6.5)	16,890 (8.6)	349 (6.7)	978 (7.7)	4,211 (8.2)	5,150 (8.6)	5,531 (8.8)	6,134 (8.8)	3,809 (7.3)	1,449 (5.1)	832 (2.7)
Diarrhea	**72,039 (19.3)**	32,093 (18.0)	39,946 (20.4)	704 (13.6)	1,712 (13.5)	9,867 (19.2)	12,769 (21.3)	13,958 (22.3)	15,536 (22.2)	10,349 (19.8)	4,402 (15.4)	2,742 (8.8)
Loss of smell or taste	**31,191 (8.3)**	12,717 (7.1)	18,474 (9.4)	67 (1.3)	1,257 (9.9)	6,828 (13.3)	6,907 (11.5)	6,361 (10.2)	5,828 (8.3)	2,930 (5.6)	775 (2.7)	238 (0.8)

Abbreviation: COVID-19 = coronavirus disease 2019.
* Status of underlying health conditions known for 287,320 persons. Status was classified as "known" if any of the following conditions were reported as present or absent: diabetes mellitus, cardiovascular disease (including hypertension), severe obesity (body mass index ≥40 kg/m^2), chronic renal disease, chronic liver disease, chronic lung disease, immunocompromising condition, autoimmune condition, neurologic condition (including neurodevelopmental, intellectual, physical, visual, or hearing impairment), psychologic/psychiatric condition, and other underlying medical condition not otherwise specified.
† Symptom status was known for 373,883 persons. Status was classified as "known" if any of the following symptoms were reported as present or absent: fever (measured >100.4°F [38°C] or subjective), cough, shortness of breath, wheezing, difficulty breathing, chills, rigors, myalgia, rhinorrhea, sore throat, chest pain, nausea or vomiting, abdominal pain, headache, fatigue, diarrhea (≥3 loose stools in a 24-hour period), or other symptom not otherwise specified on the form.
§ Responses include data from standardized fields supplemented with data from free-text fields. Information for persons with loss of smell or taste was exclusively extracted from a free-text field; therefore, persons exhibiting this symptom were likely underreported.
¶ Includes persons with reported hypertension.
** Includes all persons with at least one of these symptoms reported.
†† Persons were considered to have a fever if information on either measured or subjective fever variables if "yes" was reported for either variable.

TABLE 3. Reported hospitalizations,*,† intensive care unit (ICU) admissions,§ and deaths¶ among laboratory-confirmed COVID-19 patients with and without reported underlying health conditions, by sex and age — United States, January 22–May 30, 2020**

	Outcome, no./total no. (%)††								
	Reported hospitalizations*,† (including ICU)			Reported ICU admission§			Reported deaths¶		
Characteristic (no.)	Among all patients	Among patients with reported underlying health conditions	Among patients with no reported underlying health conditions	Among all patients	Among patients with reported underlying health conditions	Among patients with no reported underlying health conditions	Among all patients	Among patients with reported underlying health conditions	Among patients with no reported underlying health conditions
Sex									
Male (646,358)	101,133/646,358 (15.6)	49,503/96,839 (51.1)	3,596/42,048 (8.6)	18,394/646,358 (2.8)	10,302/96,839 (10.6)	864/42,048 (2.1)	38,773/646,358 (6.0)	21,667/96,839 (22.4)	724/42,048 (1.7)
Female (674,130)	83,540/674,130 (12.4)	40,698/102,040 (39.9)	3,087/46,393 (6.7)	11,443/674,130 (1.7)	6,672/102,040 (6.5)	479/46,393 (1.0)	32,343/674,130 (4.8)	17,145/102,040 (16.8)	707/46,393 (1.5)
Age group (yrs)									
≤9 (20,458)	848/20,458 (4.1)	138/619 (22.3)	84/2,277 (3.7)	141/20,458 (0.7)	31/619 (5.0)	16/2,277 (0.7)	13/20,458 (0.1)	4/619 (0.6)	2/2,277 (0.1)
10–19 (49,245)	1,234/49,245 (2.5)	309/2,076 (14.9)	115/5,047 (2.3)	216/49,245 (0.4)	72/2,076 (3.5)	17/5,047 (0.3)	33/49,245 (0.1)	16/2,076 (0.8)	4/5,047 (0.1)
20–29 (182,469)	6,704/182,469 (3.7)	1,559/8,906 (17.5)	498/18,530 (2.7)	864/182,469 (0.5)	300/8,906 (3.4)	56/18,530 (0.3)	273/182,469 (0.1)	122/8,906 (1.4)	24/18,530 (0.1)
30–39 (214,849)	12,570/214,849 (5.9)	3,596/14,854 (24.2)	828/18,629 (4.4)	1,879/214,849 (0.9)	787/14,854 (5.3)	135/18,629 (0.7)	852/214,849 (0.4)	411/14,854 (2.8)	21/18,629 (0.1)
40–49 (219,139)	19,318/219,139 (8.8)	7,151/24,161 (29.6)	1,057/16,411 (6.4)	3,316/219,139 (1.5)	1,540/24,161 (6.4)	208/16,411 (1.3)	2,083/219,139 (1.0)	1,077/24,161 (4.5)	58/16,411 (0.4)
50–59 (235,774)	31,588/235,774 (13.4)	14,639/40,297 (36.3)	1,380/14,420 (9.6)	5,986/235,774 (2.5)	3,335/40,297 (8.3)	296/14,420 (2.1)	5,639/235,774 (2.4)	3,158/40,297 (7.8)	131/14,420 (0.9)
60–69 (179,007)	39,422/179,007 (22.0)	21,064/42,206 (49.9)	1,216/7,919 (15.4)	7,403/179,007 (4.1)	4,588/42,206 (10.9)	291/7,919 (3.7)	11,947/179,007 (6.7)	7,050/42,206 (16.7)	187/7,919 (2.4)
70–79 (105,252)	35,844/105,252 (34.1)	20,451/31,601 (64.7)	780/2,799 (27.9)	5,939/105,252 (5.6)	3,771/31,601 (11.9)	199/2,799 (7.1)	17,510/105,252 (16.6)	10,008/31,601 (31.7)	286/2,799 (10.2)
≥80 (114,295)	37,145/114,295 (32.5)	21,294/34,159 (62.3)	725/2,409 (30.1)	4,093/114,295 (3.6)	2,550/34,159 (7.5)	125/2,409 (5.2)	32,766/114,295 (28.7)	16,966/34,159 (49.7)	718/2,409 (29.8)
Total (1,320,488)	**184,673/1,320,488 (14.0)**	**90,201/198,879 (45.4)**	**6,683/88,441 (7.6)**	**29,837/1,320,488 (2.3)**	**16,974/198,879 (8.5)**	**1,343/88,441 (1.5)**	**71,116/1,320,488 (5.4)**	**38,812/198,879 (19.5)**	**1,431/88,441 (1.6)**

Abbreviation: COVID-19 = coronavirus disease 2019.

* Hospitalization status was known for 600,860 (46%). Among 184,673 hospitalized patients, the presence of underlying health conditions was known for 96,884 (53%).

† Includes reported ICU admissions.

§ ICU admission status was known for 186,563 (14%) patients among the total case population, representing 34% of hospitalized patients. Among 29,837 patients admitted to the ICU, the status of underlying health conditions was known for 18,317 (61%).

¶ Death outcomes were known for 480,565 (36%) patients. Among 71,116 reported deaths through case surveillance, the status of underlying health conditions was known for 40,243 (57%) patients.

** Status of underlying health conditions was known for 287,320 (22%) patients. Status was classified as "known" if any of the following conditions were noted as present or absent: diabetes mellitus, cardiovascular disease including hypertension, severe obesity body mass index ≥40 kg/m^2, chronic renal disease, chronic liver disease, chronic lung disease, any immunocompromising condition, any autoimmune condition, any neurologic condition including neurodevelopmental, intellectual, physical, visual, or hearing impairment, any psychologic/psychiatric condition, and any other underlying medical condition not otherwise specified.

†† Outcomes were calculated as the proportion of persons reported to be hospitalized, admitted to an ICU, or who died among total in the demographic group. Outcome underreporting could result from outcomes that occurred but were not reported through national case surveillance or through clinical progression to severe outcomes that occurred after time of report.

JHU might be attributable to differences in reporting practices to CDC and jurisdictional websites accessed by JHU.

Reported cumulative incidence in the case surveillance population among persons aged ≥20 years is notably higher than that among younger persons. The lower incidence in persons aged ≤19 years could be attributable to undiagnosed milder or asymptomatic illnesses among this age group that were not reported. Incidence in persons aged ≥80 years was nearly double that in persons aged 70–79 years.

Among cases with known race and ethnicity, 33% of persons were Hispanic, 22% were black, and 1.3% were AI/AN. These findings suggest that persons in these groups, who account for 18%, 13%, and 0.7% of the U.S. population, respectively, are disproportionately affected by the COVID-19 pandemic. The proportion of missing race and ethnicity data limits the conclusions that can be drawn from descriptive analyses; however, these findings are consistent with an analysis of COVID-19–Associated Hospitalization Surveillance Network (COVID-NET)††††† data that found higher proportions of black and Hispanic persons among hospitalized COVID-19 patients than were in the overall population (*4*). The completeness of race and ethnicity variables in case surveillance has increased from 20% to >40% from April 2 to June 2. Although reporting of race and ethnicity continues to improve, more complete data might be available in aggregate on jurisdictional websites or through sources like the COVID Tracking Project's COVID Racial Data Tracker.§§§§§

††††† COVID-Net is a population-based surveillance system that collects data on laboratory-confirmed COVID-19–associated hospitalizations (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html).

§§§§§ The COVID Tracking Project is *The Atlantic's* volunteer organization to collect and publish U.S. COVID-19 data (https://covidtracking.com/race/dashboard).

The data in this report show that the prevalence of reported symptoms varied by age group but was similar among males and females. Fewer than 5% of persons were reported to be asymptomatic when symptom data were submitted. Persons without symptoms might be less likely to be tested for COVID-19 because initial guidance recommended testing of only symptomatic persons and was hospital-based. Guidance on testing has evolved throughout the response.¶¶¶¶¶ Whereas incidence among males and females was similar overall, severe outcomes were more commonly reported among males. Prevalence of reported severe outcomes increased with age; the percentages of hospitalizations, ICU admissions, and deaths were highest among persons aged ≥70 years, regardless of underlying conditions, and lowest among those aged ≤19 years. Hospitalizations were six times higher and deaths 12 times higher among those with reported underlying conditions compared with those with none reported. These findings are consistent with previous reports that found that severe outcomes increased with age and underlying condition, and males were hospitalized at a higher rate than were females (*2*,*4*,*5*).

The findings in this report are subject to at least three limitations. First, case surveillance data represent a subset of the total cases of COVID-19 in the United States; not every case in the community is captured through testing and information collected might be limited if persons are unavailable or unwilling to participate in case investigations or if medical records are unavailable for data extraction. Reported cumulative incidence, although comparable across age and sex groups within the case surveillance population, are underestimates of the U.S. cumulative incidence of COVID-19. Second, reported frequencies of individual symptoms and underlying health conditions presented from case surveillance likely underestimate the true prevalence because of missing data. Finally, asymptomatic cases are not captured well in case surveillance. Asymptomatic persons are unlikely to seek testing unless they are identified through active screening (e.g., contact tracing), and, because of limitations in testing capacity and in accordance with guidance, investigation of symptomatic persons is prioritized. Increased identification and reporting of asymptomatic cases could affect patterns described in this report.

Similar to earlier reports on COVID-19 case surveillance, severe outcomes were more commonly reported among persons who were older and those with underlying health conditions (*1*). Findings in this report align with demographic and severe outcome trends identified through COVID-NET (*4*). Findings from case surveillance are evaluated along with enhanced surveillance data and serologic survey results to provide a comprehensive picture of COVID-19 trends, and differences in proportion of cases by racial and ethnic groups should continue to be examined in enhanced surveillance to better understand populations at highest risk.

¶¶¶¶¶ https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html.

Summary

What is already known about this topic?

Surveillance data reported to CDC through April 2020 indicated that COVID-19 leads to severe outcomes in older adults and those with underlying health conditions.

What is added by this report?

As of May 30, 2020, among COVID-19 cases, the most common underlying health conditions were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Hospitalizations were six times higher and deaths 12 times higher among those with reported underlying conditions compared with those with none reported.

What are the implications for public health practice?

Surveillance at all levels of government, and its continued modernization, is critical for monitoring COVID-19 trends and identifying groups at risk for infection and severe outcomes. These findings highlight the continued need for community mitigation strategies, especially for vulnerable populations, to slow COVID-19 transmission.

Since the U.S. COVID-19 response began in January, CDC has built on existing surveillance capacity to monitor the impact of illness nationally. Collection of detailed case data is a resource-intensive public health activity, regardless of disease incidence. The high incidence of COVID-19 has highlighted limitations of traditional public health case surveillance approaches to provide real-time intelligence and supports the need for continued innovation and modernization. Despite limitations, national case surveillance of COVID-19 serves a critical role in the U.S. COVID-19 response: these data demonstrate that the COVID-19 pandemic is an ongoing public health crisis in the United States that continues to affect all populations and result in severe outcomes including death. National case surveillance findings provide important information for targeted enhanced surveillance efforts and development of interventions critical to the U.S. COVID-19 response.

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[1]CDC COVID-19 Emergency Response.

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EXHIBIT 3

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C2-21-16
Baltimore, Maryland 21244-1850

CENTERS FOR MEDICARE & MEDICAID SERVICES

Center for Clinical Standards and Quality/Quality, Safety & Oversight Group

Ref: QSO-20-13-Hospitals-*CAHs*
(REVISED)

DATE: **March 30, 2020**

TO: State Survey Agency Directors

FROM: Director
Quality, Safety & Oversight Group

SUBJECT: Guidance for Infection Control and Prevention *of* Coronavirus Disease (COVID-19) *in Hospitals, Psychiatric Hospitals, and Critical Access Hospitals (CAHs)*: FAQs, Considerations for Patient Triage, Placement, *Limits to Visitation and Availability of 1135 waivers.*

Memorandum Summary

- ***The Centers for Medicare & Medicaid Services (CMS) is committed*** to taking critical steps to ensure America's health care facilities and clinical laboratories are prepared to respond to the threat of the COVID-19.
- ***Coordination with the Centers for Disease Control (CDC) and local public health departments*** - We encourage all hospitals, *psychiatric hospitals, and CAHs* to monitor the CDC website for information and resources and contact their local health department when needed (CDC Resources for Health Care Facilities: https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/index.html).
- ***Hospital/CAH Guidance and Actions*** - CMS regulations and guidance support hospitals *and CAHs* taking appropriate action to address potential and confirmed COVID-19 cases to mitigate transmission *and prepare for community spread* transmission, including screening, discharge and transfers from the hospital, *mitigation of staffing crises,* and visitation.
- ***Hospital/CAH Flexibilities*** – *Under Section 1135 of the Social Security Act (Act), CMS has waived a number of hospital/CAH requirements following the President's declaration of a national state of emergency and the Secretary's declaration of a Public Health Emergency to facilitate increasing hospital capacity, establishing alternate care sites, and removing administrative burdens.*

Background

CMS is committed to the protection of patients and residents of healthcare facilities from the spread of infectious disease. This memorandum responds to questions we have received and provides important guidance for hospitals, *psychiatric hospitals*, and critical access hospitals (CAHs) in addressing the COVID-19 outbreak and minimizing transmission to other

individuals. Specifically, we address FAQs related to optimizing patient placement, with the goal of addressing the needs of the individual patient while protecting other patients and healthcare workers.

Guidance

Hospitals*, psychiatric hospitals, and CAHs* should monitor the Centers for Disease Control and Prevention's (CDC) website (https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html) for up-to-date information and resources *for the mitigation of transmission of COVID-19 for both inpatient and outpatient facilities.* They should contact their local health department if they have questions or suspect a patient or healthcare provider has COVID-19. Hospitals*, psychiatric hospitals, and CAHs* should have plans for monitoring healthcare personnel with exposure to patients with known or suspected COVID-19. Also, in light of limited staffing options, there should be a plan for how exposed or infected healthcare personnel may return to work. Additional information about monitoring healthcare personnel *and returning to work* is available here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html; https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/hcp-return-work.html

Hospital, Psychiatric Hospital, and CAH Capacity for Acute Inpatient Care and Excluded Psychiatric and Rehabilitation Units

CMS has waived a number of requirements under Section 1135 for all hospitals including CAHs and psychiatric hospitals. Current information on 1135 waivers available to all hospitals/CAHs and psychiatric hospitals can be found at: https://www.cms.gov/files/document/covid19-emergency-declaration-health-care-providers-fact-sheet.pdf and https://www.cms.gov/About-CMS/Agency-Information/Emergency/EPRO/Current-Emergencies/Current-Emergencies-page

Case-by-case waivers may be requested at 1135waiver@cms.hhs.gov.

Guidance for *Mitigating Transmission and Preparing for Community Spread* of COVID-19 Addressing Patient Triage, Placement of Patients with known or suspected COVID-19, *Mitigation of Staffing Shortages (due to COVID-19 patient surges and/or staff becoming infected) and Expanded Visitation Recommendations*

If healthcare personnel have been exposed or infected with COVID-19, when can they return to work to prevent staffing shortages?

According to CDC, in hospitals where testing is available, it is suggested that test-based strategies are preferred.

1. *Test-based strategy. Personnel should be excluded from work until:*

    - *Resolution of fever without the use of fever-reducing medications,* ***and***
    - *Improvement in respiratory symptoms (e.g., cough, shortness of breath),* ***and***
    - *Negative results of an FDA Emergency Use Authorized molecular assay for COVID-19 from at least two consecutive nasopharyngeal swab specimens collected ≥24 hours apart (total of two negative specimens)[1]. See Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens for 2019 Novel Coronavirus (2019-nCoV).*

2. *Non-test-based strategy. Personnel should be excluded from work until:*

    - *At least 3 days (72 hours) have passed since recovery, defined as resolution of fever without the use of fever-reducing medications **and** improvement in respiratory symptoms (e.g., cough, shortness of breath); **and**,*
    - *At least 7 days have passed since symptoms first appeared.*

If healthcare personnel were never tested for COVID-19 but have an alternate diagnosis such has having tested positive for influenza, criteria for return to work should be based on existing guidance for that diagnosis.

Are there special considerations for previously exposed or infected healthcare personnel when returning to the workplace?

Before returning to work, exposed healthcare personnel should:

- *Consult with their occupational health program, be monitored for symptoms, and seek re-evaluation from occupational health if fever and/or respiratory symptoms recur or worsen.*

For more information on self-monitoring please see: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html

Healthcare personnel with confirmed or suspected COVID-19 should consult with their occupational health program and follow the CDC Interim guidance on return to work. https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/hcp-return-work.html

What additional measures should a hospital, psychiatric hospital, or CAH consider for the mitigation of transmission in outpatient settings?

- *Reschedule non-urgent outpatient visits as necessary.*
- *Consider reaching out to patients who may be at a higher risk of COVID-19-related complications such as the elderly, those with medical co-morbidities, and potentially other persons who are at higher risk for complications from respiratory diseases, such as pregnant women to ensure adherence to current medications and therapeutic regimens, confirm they have sufficient medication refills, and provide instructions to notify their provider by phone if they become ill.*
- *Consider accelerating the timing of high priority screening and intervention needs for the short-term, in anticipation of the possible need to manage an influx of COVID-19 patients in the weeks to come.*
- *Symptomatic patients who need to be seen in a clinical setting should be asked to call before they leave home, so staff are ready to receive them using appropriate infection control practices, including providing a mask for the potentially infectious patient before or immediately upon entry into the healthcare facility, and personal protective equipment for the healthcare personnel.*

What additional measures should a hospital, psychiatric hospital or CAH consider for the mitigation of transmission in inpatient settings?

- *Reschedule elective surgeries, procedures, and other visits as necessary.*

- *Shift elective urgent inpatient diagnostic and surgical procedures to outpatient settings, when feasible.*
- *Maintain social distancing of at least six feet during group therapy interactions.*
- *Limit visitors to COVID-19 positive patients and persons under investigation (PUI).*
- *Plan for a surge of critically ill patients and identify additional space to care for these patients. Include options for:*
    - *Using alternate and separate spaces in the ER, ICUs, and other patient care areas to manage known or suspected COVID-19 patients.*
    - *Separating known or suspected COVID-19 patients from other patients ("cohorting").*
    - *Identifying dedicated staff to care for COVID-19 patients.*

Can an acute care inpatient be admitted to an excluded psychiatric unit to temporarily expand bed capacity?

Yes, CMS will allow acute care hospitals/CAHs with excluded distinct part psychiatric units that need to relocate acute care inpatients to excluded distinct part psychiatric units to provide care for overflow due to COVID-19 patients.

Can an acute care inpatient be admitted to an excluded rehabilitation unit to temporarily expand bed capacity?

Yes, CMS will allow acute care hospitals/CAHs with excluded distinct part inpatient rehabilitation units that need to relocate acute care inpatients to excluded distinct part rehabilitation units in order to provide care for overflow due to COVID-19 patients. The distinct part unit's bed must be appropriate for the acute care inpatient.

Can an inpatient of an excluded rehabilitation unit be admitted to an acute care inpatient unit to temporarily expand bed capacity?

Yes, CMS will allow acute care hospitals/CAHs with excluded distinct part inpatient rehabilitation units that relocate their inpatients to an acute care bed and unit units to provide care for overflow due to COVID-19 patients. This waiver may be utilized where the hospital/CAH's acute care beds are appropriate for providing care to rehabilitation patients and such patients continue to receive intensive rehabilitation services.

Can an excluded unit psychiatric inpatient be admitted to an acute care inpatient unit to expand bed capacity?

Yes, CMS will allow acute care hospitals/CAHs with excluded distinct part inpatient psychiatric units to relocate their inpatients to an acute care bed and unit to provide care for overflow due to COVID-19 patients. This waiver may be used when the hospital/CAH's acute care beds are appropriate for psychiatric patients and the staff and environment are conducive to safe care. For psychiatric patients, this includes assessment of the acute care bed and unit location to ensure those patients at risk of harm to self and others receive safe and appropriate care.

Which patients are at risk for severe disease for COVID-19?

Based upon CDC data *https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/high-risk-complications.html*, older adults and those with underlying chronic medical conditions or immunocompromised state may be most at risk for severe outcomes. This should be considered in the decision to monitor the patient as an outpatient or inpatient.

How should facilities screen visitors and patients for COVID-19?

Hospitals*, psychiatric hospitals, and CAHs* should identify visitors and patients at risk for having COVID-19 infection before or immediately upon arrival to the healthcare facility. They should ask patients about the following:

1. *Signs or symptoms of a respiratory infection, such as a fever, cough, or difficulty breathing.*
2. *Contact with a person who is positive for COVID-19 or with someone who is considered a PUI or someone who is ill with respiratory illness.*
3. *Travel within the last 14 days to areas with widespread or ongoing COVID-19 community spread. For updated information on countries and restricted areas within the U.S., visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/after-travel-precautions.html.*
4. *Residence or working in a community where community-based spread of COVID-19 is occurring. For more information on mitigation plans for communities identified to be at risk, visit: https://www.cdc.gov/coronavirus/2019-ncov/community/index.html.*

For patients, implement respiratory hygiene and cough etiquette (i.e., placing a facemask over the patient's nose and mouth if that has not already been done) and isolate the patient in an examination room with the door closed. If the patient cannot be immediately moved to an examination room, ensure they are not allowed to wait among other patients seeking care. Identify a separate, well-ventilated space that allows waiting patients to be separated by 6 or more feet, with easy access to respiratory hygiene supplies. In some settings, medically-stable patients might opt to wait in a personal vehicle or outside the healthcare facility where they can be contacted by mobile phone when it is their turn to be evaluated.

Inform infection prevention and control services, local and state public health authorities, and other healthcare facility staff as appropriate about the presence of a person under investigation for COVID-19. Additional guidance for evaluating patients in U.S. for COVID-19 infection can be found on the CDC COVID-19 website. *For more specific guidance see resource links*.

Provide supplies for respiratory hygiene and cough etiquette, including 60%-95% alcohol-based hand sanitizer (ABHS), tissues, no touch receptacles for disposal, facemasks, and tissues at healthcare facility entrances, waiting rooms, patient check-ins, etc.

How should facilities monitor or restrict healthcare facility staff?

The same screening performed for visitors should be performed for hospital*, psychiatric hospital, and CAH* staff.

- Healthcare providers (HCP) who have signs and symptoms of a respiratory infection should not report to work.
- Any staff that develop signs and symptoms of a respiratory infection while on-the-job, should:

- Immediately stop work, put on a facemask, and self-isolate at home.
- Inform the hospital*, psychiatric hospital, or CAH*'s infection *control professional/*preventionist and include information on individuals, equipment, and locations the person came in contact with.
- Contact and follow the local health department recommendations for next steps such as testing and locations for treatment.

- Refer to the CDC guidance for exposures that might warrant restricting asymptomatic healthcare personnel from reporting to work (https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html).
- *Report cases of illness to their supervisor, employee health service, and/or occupational health clinic. Employees should also consult their healthcare provider if they are experiencing signs/symptoms consistent with COVID-19*

Hospitals*, psychiatric hospitals, and CAHs* should contact their local health department for questions, and frequently review the CDC website dedicated to COVID-19 for health care professionals (https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html).

Can hospitals continue to procure organs for organ donation?

Yes. Ensuring that individuals have continued access to life-saving organs is critical. We understand that hospitals are preparing for a surge in COVID-19 patients; however, we would ask that donor hospitals continue with normal operations in regards to allowing organ procurement coordinators into hospitals to discuss organ donation with families wherever possible. Hospital and Organ Procurement Organization (OPO) leadership should communicate on risk assessments in their communities and any potential impacts for organ recovery operations.

What are recommended infection prevention and control practices, including considerations for patient placement, when evaluating and care for patients with known or suspected COVID-19?

Recommendations for patient placement and other detailed infection prevention and control recommendations regarding hand hygiene, Transmission-Based Precautions, environmental cleaning and disinfection, managing visitors, and monitoring and managing healthcare personnel are available in the CDC Interim Infection Prevention and Control Recommendations for Patients with Confirmed Coronavirus Disease 2019 (COVID-19) or Persons under Investigation for COVID-19 in Healthcare Settings.

Do all patients with known or suspected COVID-19 infection require hospitalization?

No. Patients may not require hospitalization and can be managed at home if they are able to comply with monitoring requests. More information is available here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home-care.html

Are there specific considerations for patients requiring diagnostic or therapeutic interventions?

Patients with known or suspected COVID-19 should continue to receive the intervention appropriate for the severity of their illness and overall clinical condition. Because some

procedures such as intubation create high risks for transmission additional precautions include: 1) HCP should wear all recommended *personal protective equipment (PPE),* 2) the number of HCP present should be limited to essential personnel, and 3) the room should be cleaned and disinfected in accordance with environmental infection control guidelines.

Additional information about performing aerosol-generating procedures is available here: https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html

Please note that CDC has issued updated strategies for optimizing the use of facemasks. https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/face-masks.html.

When is it safe to discontinue Transmission-Based Precautions for hospitalized patients with COVID-19?

The decision to discontinue Transmission-Based Precautions for hospitalized patients with COVID-19 should be made on a case-by-case basis in consultation with clinicians, infection prevention and control specialists, and public health officials. This decision should consider disease severity, illness signs and symptoms, and results of laboratory testing for COVID-19 in respiratory specimens. More detailed information about criteria to discontinue Transmission-Based Precautions are available here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized- patients.html.

What are the considerations for discharge to a subsequent care location for patients with COVID-19?

The decision to discharge a patient from the hospital*, psychiatric hospital, or CAH* should be made based on the clinical condition of the patient. If Transmission-Based Precautions must be continued in the subsequent setting, the receiving facility must be able to implement all recommended infection prevention and control recommendations.

Although COVID-19 patients with mild symptoms may be managed at home, the decision to discharge to home should consider the patient's ability to adhere to isolation recommendations, as well as the potential risk of secondary transmission to household members with immunocompromising conditions. *Special consideration should be given to patients with psychiatric or cognitive disabilities to ensure they are able to adhere to the COVID-19 discharge recommendations and fully comprehend the significance of the precautions, or they have a family member or significant other involved to assist with these restrictions.* More information is available here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home-care.html

What are the implications of the Medicare Hospital*, psychiatric hospital, Psychiatric Hospital, and CAH* Discharge Planning Regulations for Patients with COVID-19?

Medicare's Discharge Planning Regulations (which were updated in November 2019) require that *the* hospital*, psychiatric hospital, or CAH* assess the patient's needs for post-hospital*, psychiatric hospital or CAH* services, and the availability of such services. When a patient is discharged, all necessary medical information (including communicable diseases) must be provided to any post-

acute service provider. For COVID-19 patients, this must be communicated to the receiving service provider prior to the discharge/transfer and to the healthcare transport personnel.

Can hospitals*, psychiatric hospital, and CAHs* restrict visitation of patients?

Medicare regulations require a hospital*, psychiatric hospital, or CAH* to have written policies and procedures regarding the visitation rights of patients, including those setting forth any clinically necessary or reasonable restriction or limitation that the hospital*, psychiatric hospital, or CAH* may need to place on such rights and the reasons for the clinical restriction or limitation. CMS sub-regulatory guidance identifies infection control concern as an example of when clinical restrictions may be warranted. Patients must be informed of his/her visitation rights and the clinical restrictions or limitations on visitation.

The development of such policies and procedures require hospitals to focus efforts on preventing and controlling infections, not just between patients and personnel, but also between individuals across the entire hospital*, psychiatric hospital, and CAH* setting (for example, among patients, staff, and visitors) as well as between the hospital*, psychiatric hospital, and CAH* and other healthcare institutions and settings and between patients and the healthcare environment. Hospitals*, psychiatric hospitals, and CAHs* should work with their local, state, and federal public health agencies to develop appropriate preparedness and response strategies for communicable disease threats.

Limiting visitors and individuals: Expanded recommendations:

CMS is providing the following expanded guidance for hospitals, psychiatric hospitals, and CAHs located in States with COVID-19 cases are present to prevent the spread of COVID-19:

a) *Visitors should receive the same screening as patients, including whether they have had:*
   - *Fever or symptoms of a respiratory infection, such as a cough and difficulty breathing.*
   - *International travel within the last 14 days to CDC Level 3 risk countries. For updated information on restricted countries visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/index.html and for considerations after recent international travel visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/after-travel-precautions.html*
   - *Recent trips (within the last 30 days) on cruise ships. For updated information on recent cruise ship travel, visit the CDC website: https://wwwnc.cdc.gov/travel/page/covid-19-cruise-ship*
   - *Contact with someone with known or suspected COVID-19 or ill with respiratory illness.*
   - *Travel in the last 14 days within the United States to restricted areas. Information and guidance on restricted areas within the US, visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/travel-in-the-us.html*

b) *Healthcare facilities should set limitations on visitation. For example, limitations may include restricting the number of visitors per patient, or limiting visitors to only those that provide assistance to the patient, or limiting visitors under a certain age.*

c) *Facilities must ensure patients have adequate and lawful access to chaplains or clergy in conformance with the Religious Freedom Restoration Act and Religious Land Use and Institutionalized Persons Act.*

d) *Healthcare facilities should provide signage at entrances for screening individuals, provide temperature checks/ ask about fever, and encourage frequent hand washing and use of hand sanitizer before entering the facility and before and after entering patient rooms*

e) If visiting and not seeking medical treatment themselves, individuals with fevers, cough, difficulty breathing, body aches or runny nose or those who are not following infection control guidance should be restricted from entry.

f) Facilities should instruct visitors to limit their movement within the facility by reducing such things as walking the halls or trips to the cafeteria.

g) Facilities should establish limited entry points for all visitors and/or establish alternative sites for screening prior to entry.

h) Facilities can implement measures to:

- *Increase communication with families (phone, social media, etc.)*
- *Potentially offer a hotline with a recording that is updated at set times so families can stay current on the facility's general status.*
- *If appropriate, consider offering telephonic screening of recent travel and wellness prior to coming in for scheduled appointments. This may help limit the amount of visitor movement throughout the organization and congestion at entry points.*

i) Consider closing common visiting areas and encouraging patients to visit with loved ones in their patient rooms.

CDC Resources:

- *Coronavirus Disease 2019 (COVID-19) Hospital Preparedness Assessment Tool https://www.cdc.gov/coronavirus/2019-ncov/hcp/hcp-hospital-checklist.html*
- CDC Resources for Health Care Facilities: https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/index.html
- CDC Updates: https://www.cdc.gov/coronavirus/2019-ncov/whats-new-all.html
- CDC FAQ for COVID-19**:** https://www.cdc.gov/coronavirus/2019-ncov/infection-control/infection-prevention-control-faq.html
- CDC Interim Infection Prevention and Control Recommendations for Patients with Confirmed Coronavirus Disease 2019 (COVID19) or Persons Under Investigation for COVID-19 in Healthcare Settings.: https://www.cdc.gov/coronavirus/2019-ncov/infection- control/controrecommendations.html?CDC_AA_refVal=. https%3A%2F%2Fwww.c dc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Finfection-control.html
- Health Department Directories: https://www.naccho.org/membership/lhd-directory

CDC Updates:

https://www.cdc.gov/coronavirus/2019-ncov/whats-new-all.html

Mental Health Resources:

SAMHSA has developed guidelines for Psychiatric Hospitals which can be found here: https://www.samhsa.gov/sites/default/files/covid19-interim-considerations-for-state-psychiatric-hospitals.pdf

CMS Resources:

CMS has additional guidance which may be beneficial to hospitals*, psychiatric hospitals, and*

CAHs related to *screening patients for COVID in alternate locations, Emergency Medical Treatment and Labor Act (EMTALA)* requirements and other topics surrounding the health and safety standards during emergencies: *https://www.cms.gov/files/document/qso-20-15-hospitalcahemtala.pdf.*

The document Provider Survey and Certification Frequently Asked Questions (FAQs), Declared Public Health Emergency All-Hazards are located at https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertEmergPrep/Downloads/All-Hazards-FAQs.pdf. These FAQs are not limited to situations involving 1135 Waivers, but are all encompassing FAQs related to public health emergencies and survey activities and functions.

Contact:

Questions about this memorandum should be addressed to QSOG_EmergencyPrep@cms.hhs.gov. Questions about COVID-19 guidance/screening criteria should be addressed to the State Epidemiologist or other responsible state or local public healt/h officials in your state.

Effective Date:

Immediately. This policy should be communicated with all survey and certification staff, their managers and the State/Regional Office training coordinators immediately.

/s/
David R. Wright

cc: Survey and Operations Group Management

EXHIBIT 4

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C2-21-16
Baltimore, Maryland 21244-1850

CENTERS FOR MEDICARE & MEDICAID SERVICES

Center for Clinical Standards and Quality/Quality, Safety & Oversight Group

Ref: QSO-20-23-ICF/IID & PRTF

DATE: **March 30, 2020**

TO: State Survey Agency Directors

FROM: Director
Quality, Safety & Oversight Group

SUBJECT: Guidance for Infection Control and Prevention of Coronavirus Disease 2019 (COVID-19) in Intermediate Care Facilities for Individuals with Intellectual Disabilities (ICF/IIDs) and Psychiatric Residential Treatment Facilities (PRTFs)

Memorandum Summary

- ***CMS is committed*** to taking critical steps to ensure America's health care facilities and clinical laboratories are prepared to respond to the threat of the COVID-19.
- **Guidance for Infection Control and Prevention of COVID-19 -** CMS is providing additional guidance to intermediate care facilities for individuals with intellectual disabilities (ICF/IIDs) to help them improve their infection control and prevention practices to prevent the transmission of COVID-19, including revised guidance for visitation.
- **Coordination with the Centers for Disease Control (CDC) and public health departments -** We encourage all ICF/IIDs and Psychiatric Residential Treatment Facilities (PRTFs) to monitor the CDC website for information and resources and contact their health department when needed (CDC Resources for Health Care Facilities: https://www.cdc.gov/coronavirus/2019- ncov/healthcare-facilities/index.html).

Background

CMS is responsible for ensuring the health and safety of ICF/IID and PRTF clients/residents by enforcing the standards required to help each client/resident attain or maintain their highest level of well-being. In light of the recent spread of COVID-19, we are providing additional guidance to ICF/IIDs and PRTFs to help control and prevent the spread of the virus SARS-CoV-2 and the disease it causes, COVID-19.

Guidance

Facility staff should regularly monitor the CDC website for information and resources (https://www.cdc.gov/coronavirus/2019-ncov/index.html). They should contact their state

health agency if they have questions or suspect a client/resident of an ICF/IID or PRTF has COVID-19. Per CDC, prompt detection, triage and isolation of potentially infectious clients/residents are essential to prevent unnecessary exposures among clients/residents, healthcare personnel, and visitors at the facility. Therefore, facilities should continue to be vigilant in identifying any possible infected individuals. Facilities should consider frequent monitoring for potential symptoms of respiratory infection as needed throughout the day. The following link can be used for guidance on screening visitors and monitoring or restricting facility health care staff: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/index.html.

Furthermore, we encourage facilities to take advantage of resources that have been made available by CDC and CMS to train and prepare staff to improve infection control and prevention practices See CDC and CMS resource links: https://www.cdc.gov/longtermcare/index.html and https://www.medicaid.gov/state-resource-center/disaster-response-toolkit/federal-disaster-resources/index.html. Lastly, facilities should maintain a person-centered approach to care. This includes communicating effectively with clients/residents, client/resident representatives and/or their family, and understanding their individual needs and goals of care. Staff should adjust communication about the COVID-19 disease and the underlying virus and SARS-CoV-2 infection prevention and control procedures being taken by the facility, and any potential modifications or restrictions to clients/residents' daily routine as appropriate to the client/resident/family member's age and preferred language, as well as their, emotional, psychological, and functioning status while using required auxiliary aides and services. Communications should not be limited based on an individual's functioning level; clients/residents should receive information regardless of functioning level.

Facilities experiencing any new respiratory illnesses (regardless of suspected etiology) among clients/residents or healthcare personnel should be initially evaluated by their facility medical professional and if deemed necessary contact their state health agency for further guidance. For information on your state's health agency link: https://www.cdc.gov/publichealthgateway/healthdirectories/healthdepartments.html.

Guidance for Limiting the Transmission of COVID-19 for ICF/IIDs and PRTFs

What flexibilities to the current regulations are available to ICF/IID and PRTF providers?

Response: President Trump's declaration of a national emergency due to COVID-19 was announced on Friday, March 13, 2020 which led to the Secretary of the Department of Health and Human Services to authorize CMS to take proactive steps through emergency waivers and modifications under section 1135 of the Social Security Act (Act) and rapidly expand the Administration's aggressive efforts against COVID-19. As a result of this authority, CMS will issue blanket waivers of certain requirements and will review other individual waiver requests on a case by case basis, which will ease certain requirements for impacted providers.

How do waivers & flexibilities help?

Response: We will use the allowable flexibilities and issue waivers as needed to help those affected by an emergency or disaster. If needed, specific waivers may be retroactive to the beginning of the emergency or disaster. We can also adjust some agency policies or procedures, usually without reprogramming our systems. Additional information is available at: https://www.cms.gov/About-

CMS/Agency-Information/Emergency/EPRO/Current-Emergencies/Current-Emergencies-page

What are blanket waivers?

Response: Under Section 1135 of the Act, CMS can implement specific waivers or modifications on a "blanket" basis when a determination has been made that all similarly situated providers in the emergency area need such a waiver or modification. When a blanket waiver is issued, providers do not have to apply for an individual waiver. Blanket waivers prevent access to care gaps for beneficiaries affected by the emergency. If there is no blanket waiver in place for a specific requirement, providers can ask for an individual Section 1135 waiver by following our instructions. In addition to 1135 waivers, we may also cover certain extended care services on an emergency basis under section 1812(f) of the Social Security Act.

Has CMS issued any 1135 waivers for ICF/IID or PRTF facilities?

Response: Current information about blanket waivers are available on the CMS website at:https://www.cms.gov/files/document/covid19-emergency-declaration-health-care-providers-fact-sheet.pdf. In addition, individual case-by-case waivers may be available by submitting a request to 1135waiver@cms.hhs.gov.

In cases where ICF/IID staffing is impacted by COVID-19, will CMS temporarily waive the minimum staffing requirements for ICF/IIDs?

Response: We encourage both ICF/IID and PRTF providers to review any state licensing requirements and work with their States on flexibilities to those requirements.

As described above, an emergency waiver under section 1135 can be requested, but otherwise CMS is not waiving ICF/IID staffing requirements. Please see https://www.cms.gov/About-CMS/Agency-Information/Emergency/EPRO/Current-Emergencies/Current-Emergencies-page for the latest information on 1135 waivers specific to specific health care providers. For case-specific waivers, the facility administrator or designated representative should submit your request to 1135waiver@cms.hhs.gov.

Can ICF/IIDs combine residents of several homes if staffing is not available? If so, do ICF/IIDs need to get a facility-specific authorization to exceed their certified bed capacity?

Response: Because of the high infection rate of COVID-19 and the increased vulnerability of people with disabilities to have serious response due to complications, people should, as a rule, not be forced into settings that would increase social interaction beyond recommended levels. Instead, people should be moved into community based settings and states should take advantage of the many opportunities for addressing staffing shortages. However, for ICF/IIDs that have multiple sites under a single CMS certification number, there is flexibility in cohorting residents for purposes of mitigating transmission. We would encourage consultation with state public health agencies to address combining facilities and staffing.

For separately-certified ICF/IIDs that need to combine, they should reach out to their State to address any state licensure requirements and may also seek specific 1135 emergency waivers. In all cases, ICF/IIDs should keep clear records of individuals who are moved, and should take appropriate measures to ensure the health and safety of those individuals during transit as well as at

the new location. If ICF/IIDs determine it is in the best interest of their residents to combine facilities, they should work to minimize the impact to residents (for example, by permitting residents to bring favorite possessions, clothes, etc.). For additional information on 1135 waivers, please see the links below.

If a State is not currently broadly testing for the coronavirus, we are aware of people who have symptoms, who have tested negative for both the flu and for RSV and who have been told by their healthcare provider to go home and not get anyone else sick because the provider does not have access to the test. At what point does the facility implement exposure measures and at what point do they contact the health department and CDC in this kind of scenario?

Response: The ICF/IID should follow the guidance of their State public health department or agency, the CDC and the CMS if they have additional concerns regarding client and staff exposure. See the following links:
https://www.cdc.gov/publichealthgateway/healthdirectories/healthdepartments.html,
https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/index.html and
https://www.medicaid.gov/state-resource-center/disaster-response-toolkit/federal-disaster-resources/index.html .

How should facilities monitor or restrict health care facility staff?

Response: The same screening performed for visitors should be performed for facility staff.

- Health care providers (HCPs) who have signs and symptoms of a respiratory infection should not report to work.
- Any staff that develop signs and symptoms of a respiratory infection while on-the-job, should:
  - Immediately stop work, put on a facemask, and self-isolate at home;
  - Inform the facility's leadership, and include information on individuals, equipment, and locations the person came in contact with; and
  - Contact and follow the state health agency recommendations for next steps (e.g., testing).
- Refer to the CDC guidance for exposures that might warrant restricting asymptomatic healthcare personnel from reporting to work (https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html).

Facilities should contact their state health agency for questions, and frequently review the CDC website dedicated to COVID-19 for health care professionals (https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html).

Should ICF/IID community activities be limited in counties with confirmed COVID-19 cases for all people or should it be a person-centered decision based on the team's evaluation of the risks?

Response: Community activities should be limited in accordance with current CDC guidance and other State and Federal requirements. Nationally, the CDC has advised individuals should practice social distancing, avoid gatherings of more than10 individuals for high-risk populations and go into the community only for essential activities. https://www.cdc.gov/coronavirus/2019-ncov/community/large-events/mass-gatherings-ready-for-covid-19.html. Facilities should consider the high infection rates of COVID-19 and all geographic areas should be assumed to have high

levels of infected individuals unless proven differently based on adequate testing. States may have also imposed more restrictive limitations. The CDC guidance should not eliminate the opportunity for individuals to leave their homes. State and Federal agencies are issuing simultaneous guidance for COVID-19 and restrictive measures should be made in the context of competent, person-centered planning for each individual.

Can ICF/IID active treatment requirements be modified for COVID-19 cases?

Response: Under 42 CFR 483.440(c), a modification can be made to the client's Individual Program Plan (IPP) with the approval of the interdisciplinary team. Refer to your Emergency Preparedness (EP) policy and procedures to help address how to manage active treatment during an infection control emergency.

Can an ICF/IID utilize a day program building for quarantine, if necessary?

Response: We encourage ICF/IID programs to discuss these options with their state health agency and the State Survey Agency to address licensure issues, and to request any relevant models to the CMS 1135 waiver mailbox at 1135waiver@cms.hhs.gov and/or the appropriate CMS locations. This may also be addressed in the ICF/IID's emergency preparedness plan. We encourage active communication between the ICF/IID and day programs. There may be a number of alternate care models that ICF/IID programs could develop to separate positive COVID-19 patients from others. In all cases, ICF/IIDs should keep clear records of individuals who are moved, and should take appropriate measures to ensure the health and safety of those individuals during transit and at the new location.

How do we address the potential staffing shortage due to a 14-day quarantine for exposed health professionals who were not fully gowned and goggled which has the potential of wiping out our entire staffing [for one or more] [ICF/IID] homes?

Response: Please review the CDC website for updated information regarding exposure of Healthcare Professionals (HCPs). The CDC has provided recommendations on flexibility for asymptomatic, exposed HCPs to return to work "in selected circumstances". The CDC has established specific risk categories and provided recommendations regarding self-isolation and asymptomatic HCPs. https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html. An ICF/IID facility may request a State specific 1135 waiver as a potential solution for staffing shortages. See the following link at https://www.cms.gov/files/document/covid19-emergency-declaration-health-care-providers-fact-sheet.pdf for the latest information for health care providers on 1135 waivers. For case-specific waivers, the facility administrator or designated representative should submit a request to 1135waiver@cms.hhs.gov. Facilities should follow their Emergency Preparedness program regarding emergency staffing. Additional information about CDC guidance regarding when health care workers may return to work can be found at https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/hcp-return-work.html.

When a client/resident has tested positive for COVID-19 and we implement quarantine procedures, client rights are immediately abridged and severe behaviors are likely to occur. This could be a situation where abuse via involuntary seclusion is an issue that has to be addressed. What is the guidance from CMS on balancing the CDC expectations with the rights of the individual?

Response: The health and safety of the clients/residents, visitors, and staff are the highest priority. For clients/residents that have been found positive for COVID-19 virus, the ICF/IID EP plan and Individual Program Plan (IPP) should include what specific procedures and steps should be taken for quarantine of the client while also taking every step reasonable to protect the rights, safety and health of the infected clients/residents and as well as those of the staff/s and other clients/residents. The facility quarantine procedures and steps should be consistent with the recommendations of the state and federal health agencies.

Facilities should adhere to the infection prevention and control practices issued by the CDC. It may be appropriate to consult with your state health agency for guidance based on the unique challenges of instituting infection prevention and control with individuals with intellectual disabilities in an ICF/IID. Currently, having clients/residents in their room with the door closed is the primary recommendation by the CDC for long-term care facilities (https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/prevent-spread-in-long-term-care-facilities.html). If that is not possible, options may include having the individual wear a facemask or other covering over their nose/mouth and provide whatever space restrictions are tolerated, such as six-foot social distancing. Facilities will have to consider multiple solutions to quarantine and preparedness is key in addition to good infection control practices.

We encourage facilities to work with all clients/residents to maintain good infection control practices and to perform thorough environmental cleaning. See the CDC link for cleaning recommendations at https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/cleaning-disinfection.html. These steps may help clients/residents to better endure the stress and anxiety of confinement with less impact to their existing emotional and/or psychological disability. It will be important, to the degree possible, to allow these individuals to experience some of their daily routines, including access to outdoors, staff, and treatment while still under quarantine

How should facilities screen visitors and outside healthcare service providers?

Response: Facilities should actively screen and restrict visitation or healthcare service providers (e.g. contract therapist) by those who meet the following criteria:

1. Signs or symptoms of a respiratory infection, such as a fever, cough, or difficulty breathing.
2. Contact with someone with or under investigation for COVID-19 or ill with respiratory illness.
3. International travel within the last 14 days to countries with widespread or ongoing community spread. For updated information on countries visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/after-travel-precautions.html
4. Residence in a community where community-based spread of COVID-19 is occurring. For more information on mitigation plans for communities identified to be at risk, visit: https://www.cdc.gov/coronavirus/2019-ncov/community/index.html

For those individuals that do not meet the above criteria, facilities can allow entry but may require visitors or outside health care providers to use Personal Protective Equipment (PPE) such as facemasks as an extra precaution, as available. For those clients/residents that are not able to have visitors or outside healthcare providers visits due to having medical risk factors if they were to contract COVID-19 or for those who test positive for COVID-19, facilities should consider:
a) Offering alternative means of communication for people who would otherwise visit, such as virtual communications (phone, video-communication, etc.).

b) Creating/increasing listserv communication to update families or outside healthcare providers, such as advising to not visit.
c) Assigning staff as primary contact to families for inbound calls, and conduct regular outbound calls to keep families up to date.
d) Offering a phone line with a voice recording updated at set times (e.g., daily) with the facility's general operating status, such as when it is safe to resume visits.

When should ICF/IIDs or PRTFs consider transferring a client/resident with suspected or confirmed infection with COVID-19 to a hospital?

Response: ICF/IIDs or PRTFs with clients/residents suspected of or confirmed having COVID-19 infection should contact their state health agency for guidance. Clients/residents infected with COVID-19 may vary in severity from lack of symptoms to mild or severe symptoms or fatality. Initially, symptoms may be mild and not require transfer to a hospital as long as the facility can follow the infection prevention and control practices recommended by CDC. Facilities without an airborne infection isolation room (AIIR) are not required to transfer the client/resident assuming: 1) the client/resident does not require a higher level of care and 2) the facility can adhere to the rest of the infection prevention and control practices recommended for caring for a client/resident with COVID-19.

Facilities will want to take advantage of the telehealth benefits available to Medicare and Medicaid beneficiaries who will be able to receive various services through telehealth including common office visits, mental health counseling, and preventive health screenings. This will help ensure Medicare and Medicaid beneficiaries, who are at a higher risk for COVID-19, are able to visit with their doctor from their home, without having to go to a doctor's office or hospital which puts themselves or others at risk. Links for Medicare and Medicaid telehealth information: https://www.cms.gov/newsroom/fact-sheets/medicare-telemedicine-health-care-provider-fact-sheet and https://www.medicaid.gov/medicaid/benefits/telemedicine/index.html

Please check the following link regularly for critical updates, such as updates to CDC guidance for using PPE: https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html.

The client/resident may develop more severe symptoms and require transfer to a hospital for a higher level of care. Prior to transfer, emergency medical services and the receiving facility should be alerted to the client's/resident's diagnosis, and precautions to be taken including placing a facemask on the client/resident during transfer. If the client/resident does not require hospitalization, they can be discharged to home (in consultation with state public health authorities) if deemed medically, clinically and socially appropriate. Pending transfer or discharge, the facility should place a facemask on the client/resident and isolate him/her in a room with the door closed. If it is not possible for the client/resident to effectively wear a face mask, then a staff member with a face mask should provide supervision to ensure the client/resident stays isolated until transfer. For a client/resident that is being transferred, it will be important that staff communicate the appropriate amount of details and steps that will be followed in order to confirm the client/resident understands what to expect during the transfer. This would include providing any necessary devices, aids, and supports to help provide as much comfort and reassurance during the transfer experience.

When should an ICF/IID or a PRTF accept a client/resident who was diagnosed with COVID-

19 from a hospital?

Response: An ICF/IID or PRTF can accept a client/resident diagnosed with COVID-19 and still operate under transmission-based precautions for COVID-19 as long as the facility can follow CDC guidance for Transmission-based Precautions. If an ICF/IID or PRTF cannot follow the guidance, it must wait until these precautions are discontinued. CDC has released Interim Guidance for Discontinuing Transmission-Based Precautions or In-Home Isolation for Persons with Laboratory-confirmed COVID-19.

Information on the duration of infectivity is limited, and the CDC interim guidance has been developed with available information from similar coronaviruses. CDC states that decisions to discontinue transmission-based precautions in hospitals will be made on a case-by-case basis in consultation with clinicians, infection prevention and control specialists, and public health officials. Discontinuation will be based on multiple factors (see current CDC guidance for further details). https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html

Note: ICF/IIDs and PRTFs should admit any individuals that they would normally admit to their facility who are not symptomatic, including individuals from hospitals where a case of COVID-19 was/is present if they are able to adhere to the infection prevention and control practices recommended by the CDC.

Also, if possible, facilities should dedicate a wing or room/s for any clients/residents coming or returning from the hospital. This can serve as a step-down unit where they remain for 14 days with no symptoms.

Will ICF/IIDs or PRTFs be cited for not having the appropriate supplies?

Response: CMS is aware of that there is a scarcity of some supplies in certain areas of the country. State and Federal surveyors should not cite facilities for not having certain supplies (e.g., Personal Protective Equipment such as gowns, N95 respirators, surgical masks and alcohol-based hand rub (ABHR)) if they are having difficulty obtaining these supplies for reasons outside of their control. However, we do expect facilities to take actions to mitigate any resource shortages and show they are taking all appropriate steps to obtain the necessary supplies as soon as possible. For example, if there is a shortage of ABHR, we expect staff to practice effective hand washing with soap and water. Similarly, if there is a shortage of PPE (e.g., due to supplier(s) shortage which may be a regional or national issue), the facility should contact the state public health agency to notify them of the shortage, follow national guidelines for optimizing their supply: https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html, or identify the next best option to care for clients/residents. If a surveyor believes a facility should be cited for not having or providing the necessary supplies, the state agency should contact their CMS Location (previously termed Regional) Office.

Other considerations for facilities:

- Review CDC guidance for Infection Prevention and Control Recommendations for Patients with Confirmed COVID-19: https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control- recommendations.html
- Increase the availability and accessibility of ABHRs, tissues, no touch receptacles for

disposal, and facemasks at healthcare facility entrances, waiting rooms, client/resident check-ins, etc., and reinforce strong hand-hygiene practices.
- Ensure ABHR is accessible in all client/resident-care areas including inside and outside client/resident rooms.
- Increase signage for vigilant infection prevention, such as hand hygiene and cough etiquette.
- Properly clean, disinfect and limit sharing of medical equipment between client/residents and areas of the facility.
- Provide additional work supplies to avoid sharing (e.g., pens, pads) and disinfect workplace areas (nurse's stations, phones, internal radios, etc.).

What other resources are available for facilities to help improve infection control and prevention?

Response: CMS urges providers to take advantage of several resources that are listed below:

CDC Resources:

- CDC Resources for Health Care Facilities: https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/index.html

- CDC COVID-19 symptoms and testing: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/index.html

- CDC disinfection control cleaning: https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/cleaning-disinfection.html

- CDC Updates: https://www.cdc.gov/coronavirus/2019-ncov/whats-new-all.html

- CDC FAQ for COVID-19**:** https://www.cdc.gov/coronavirus/2019-ncov/infection-control/infection-prevention-control-faq.html

- CDC list of all state health agencies: https://www.cdc.gov/publichealthgateway/healthdirectories/healthdepartments.html

- Information on affected US locations*: https://www.cdc.gov/coronavirus/2019-ncov/cases-in-us.html*

CMS Resources:

- Medicaid Disaster Response Resources: https://www.medicaid.gov/state-resource-center/disaster-response-toolkit/federal-disaster-resources/index.html

- Medicaid telehealth benefits: https://www.medicaid.gov/medicaid/benefits/telemedicine/index.html

- CMS telemedicine for Medicare: https://www.cms.gov/newsroom/fact-sheets/medicare-telemedicine-health-care-provider-fact-sheet

- CMS ICF/IID Appendix J: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_j_intermcare.pdf

- CMS PRTF Appendix N: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_n_prtf.pdf

Advocacy Resources:

- https://selfadvocacyinfo.org/wp-content/uploads/2020/03/Plain-Language-Information-on-Coronavirus.pdf

- https://selfadvocacyinfo.org/wp-content/uploads/2020/03/Spanish-Plain-Language-Information-on-Coronavirus.pdf

Contact: Email QSOG_EmergencyPrep@cms.hhs.gov

NOTE: The situation regarding COVID-19 is still evolving worldwide and can change rapidly. Stakeholders should be prepared for guidance from CMS and other agencies (e.g., CDC) to change. Please monitor the relevant sources regularly for updates.

Effective Date: Immediately. This policy should be communicated with all survey and certification staff, their managers and the State/Regional Office training coordinators immediately.

/s/
David R. Wright

cc: Survey and Operations Group Management

EXHIBIT 5

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Coronavirus Disease 2019 (COVID-19)

People with Disabilities

Updated April 7, 2020

Print Page

COVID-19 is a new disease and we are still learning how it spreads, the severity of illness it causes, and to what extent it may spread in the United States.

Disability alone may not be related to higher risk for getting COVID-19 or having severe illness. Most people with disabilities are not inherently at higher risk for becoming infected with or having severe illness from COVID-19. However, some people with disabilities might be at a higher risk of infection or severe illness because of their underlying medical conditions. All people seem to be at higher risk of severe illness from COVID-19 if they have serious underlying chronic medical conditions like chronic lung disease, a serious heart condition, or a weakened immune system. Adults with disabilities are three times more likely than adults without disabilities to have heart disease, stroke, diabetes, or cancer than adults without disabilities.

You should talk with your healthcare provider if you have a question about your health or how your health condition is being managed.

Disability groups and risk

If you have one of the disability types listed below, you might be at increased risk of becoming infected or having unrecognized illness. You should discuss your risk of illness with your healthcare provider.

- People who have limited mobility or who cannot avoid coming into close contact with others who may be infected, such as direct support providers and family members
- People who have trouble understanding information or practicing preventive measures, such as hand washing and social distancing
- People who may not be able to communicate symptoms of illness

Protect yourself

If you or someone you care for are at higher risk of getting very sick from COVID-19, take steps to prevent getting sick. In addition to practicing everyday preventive actions, people with disabilities who have direct support providers can help protect themselves from respiratory illness in the following ways:

- Ask your direct support provider if they are experiencing any symptoms of COVID-19 or if they have been in contact with someone who has COVID-19
- Tell your direct service provider to
  - Wash their hands when they enter your home and before and after touching you (e.g., dressing, bathing/showering, transferring, toileting, feeding), handling tissues, or when changing linens or doing laundry. Learn more about proper handwashing.

- Clean and disinfect frequently touched objects and surfaces (e.g., counters, tabletops, doorknobs, bathroom fixtures, toilets, phones, keyboards, tablets, bedside tables), and equipment such as wheelchairs, scooters, walkers, canes, oxygen tanks and tubing, communication boards and other assistive devices. Refer to CDC's General Recommendations for Routine Cleaning and Disinfections of Households.

Prepare

There are some additional things people with disabilities can do to prepare during the COVID-19 outbreak:

- Plan what you will do if you or your direct support provider gets sick. Create a contact list of family, friends, neighbors and local service agencies that can provide support in case you or your direct support provider becomes ill or unavailable.
- Plan at least two ways of communicating from home and work that can be used rapidly in an emergency (e.g., landline phone, cell phone, text-messaging, email). Write down this information and keep it with you.
- Have enough household items and groceries so that you will be comfortable staying home for a few weeks, at least a 30-day supply of over the counter and prescription medicines and any medical equipment or supplies that you might need. Some health plans allow for a 90-day refill on prescription medications. Consider discussing this option with your healthcare provider. Make a photocopy of prescriptions, as this may help in obtaining medications in an emergency situation.

About COVID-19

- Coronavirus disease is a respiratory illness that can spread from person to person. The virus is thought to spread mainly between people who are in close contact with one another (within about 6 feet) through respiratory droplets produced when an infected person coughs or sneezes. It is also possible that a person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose, or eyes. For more information go to CDC's Fact Sheet- What you need to know about coronavirus disease 2019 (COVID-19) .
- Risk of infection with COVID-19 is higher for people who are in close contact with someone known to have COVID-19, such as healthcare workers, direct support providers, and household members. Other people at higher risk for infection are those who live or have recently been in an area with ongoing spread of COVID-19.

Prevention and treatment

There is currently no vaccine to protect against COVID-19. The best way to prevent infection is to take everyday preventive actions, like avoiding close contact with people who are sick and washing your hands often. There is no specific antiviral treatment for COVID-19. People with COVID-19 can seek medical care to help relieve symptoms.

More Information

People Who Need to Take Extra Precautions
People Who Are at Higher Risk for Severe Illness
Other At-Risk Populations
Direct Service Providers for People with Disabilities
Symptoms & Testing
If You Are Sick or Caring for Someone
Cases and Updates

Page last reviewed: April 7, 2020
Content source: National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases

EXHIBIT 6

COVID-19 Can Have Serious Effects on People with Mental Health Disorders

Share on Pinterest
Experts say people with severe mental illness are more likely to contract the new coronavirus and are less likely to get proper treatment for its disease, COVID-19. Getty Images

- **Experts say people with severe mental illness face serious issues during the COVID-19 pandemic.**
- **They say people with mental illness have lifestyles that increase their risk for contracting the new coronavirus.**
- **They also have more underlying health conditions that raise their risk for developing more serious cases of COVID-19 if they contract the virus.**
- **In addition, mental health facilities could face additional strain as more of their clients are diagnosed with COVID-19.**

All data and statistics are based on publicly available data at the time of publication. Some information may be out of date. Visit our coronavirus hub and follow our live updates page for the most recent information on the COVID-19 outbreak.

So far, older adults, along with those who have underlying health conditions, have been hit the hardest by the COVID-19 outbreak, with many developing severe, life threatening illnesses.

Another group that's expected to be acutely affected by the pandemic include those who have severe mental illness.

A new paperTrusted Source published in JAMA Psychiatry says a crisis is headed for the country's mental healthcare system as state psychiatric hospitals and local clinics gear up for an influx of people with COVID-19.

Mental health issues often coincide with a unique set of challenges that make it difficult for people to access even the most basic necessities, such as food, medications, stable housing, and healthcare.

Combined, all of these factors put people with severe mental illness at a much higher risk for contracting and transmitting the new coronavirus and dealing with COVID-19.

The challenges

Dr. Fumi Mitsuishi, director of the UCSF/ZSFG Division of Citywide Case Management in San Francisco, says there's a long list of challenges that put people living with psychiatric disorders — such as schizophrenia, bipolar disorder, or depression — at a higher risk from severe COVID-19.

"We're talking about a population that struggles with being housed, being able to feed themselves, being able to take care of medical issues, having enough of an income," Mitsuishi told Healthline.

Many of the people Mitsuishi sees at Citywide Case Management struggle with holding down a job. Some take home just $25 a week after paying rent.

Oftentimes, they're temporarily housed in congregate living situations, such as a shelter or center designed to get them into more permanent housing.

It's close living quarters. People sleep alongside one another and share a bathroom.

Access and underlying conditions

If one person comes down with COVID-19, there's a good chance the virus will rip through the congregated community.

Those with severe mental illness oftentimes don't have a smartphone, nor do they have laptops or access to TV, so they must rely on mental health clinicians to get the latest updates about the pandemic, according to Dr. Collin Reiff, an addiction psychiatrist at NYU Langone Health.

This also means that in a time when many mental health professionals and clinicians have started consulting with their clients remotely, those who don't have a device don't get the care they need.

“How do they suddenly make their appointments? They don’t,” Reiff said.

Layered on top of that, substance misuse is prominent among people with mental illness, Reiff told Healthline.

Substance misuse is linked to an increased susceptibilityTrusted Source to infectious diseases. It may also make people more prone to risky behavior.

Reiff says it may therefore prevent people from taking the proper safety, self-care, and social distancing measures.

The rates of smoking among those with mental illness are higher — about 60 to 70 percentTrusted Source of people with schizophrenia regularly smoke cigarettes, says Mitsuishi.

That increases their risk for asthma, chronic obstructive pulmonary disease (COPD), and other respiratory illnesses that make someone more likely to experience COVID-19 complications.

Diabetes, hypertension, heart diseaseTrusted Source, poor cholesterol — all key risk factors for serious COVID-19 complications — are also common in this population.

“Their biological age is much higher than their actual age. Our clients are in very high-risk categories for most complications from most illnesses, and COVID is one of them,” Dr. Carrie Cunningham, the medical director of Citywide Case Management, told Healthline.

Pneumonia and influenza are some of the leading causes of death in people with mental illness, largely due to underlying lung disease, Cunningham adds.

Distrust of medical community

Many people with severe mental illness also have a strong distrust for the healthcare system from previous traumatic experiences cycling in and out of hospitals.

According to Cunningham, it’s common for people with severe mental illnesses to refuse to go to the hospital.

Because of this, they put off seeking treatment even if they have symptoms. And when it comes to COVID-19, a delay in treatment can be a matter of life or death.

Then there’s the stigma of getting a respiratory disease like COVID-19. That stigma — which may manifest as a deep shame or embarrassment for getting sick — only weighs on the already heavy stigma people can carry from mental illness, which can make it even more difficult for them to lift out of their living situation.

“It’s really the stigma that leads to folks who have mental illness being shut away from opportunities. Employment is one of them, being trusted by family members, and being therefore protected and helped,” Mitsuishi said.

Strain on the system

Psychiatric units will have to rapidly adapt to the ever-changing state of the pandemic.

Among other things, nonessential activities and group therapy sessions have been postponed.

“You’re going to take medication to be stabilized, and that’s pretty much it. There are parts of the equation missing,” Reiff said.

At Citywide Case Management, Mitsuishi and Cunningham’s team has been hustling to nail down the best quarantine, screening, and caregiving procedures.

Besides the cancellation of group therapy sessions, hot meals and medications are being distributed at the front door only.

Right now, the staff has enough personal protective equipment (PPE) and is giving out about 100 meals at the front door every day. They provide about 7,000 meals a week to nearby facilities that are housing people with mental illness.

But there’s a growing fear that there will soon be shortages — of not just PPE but food and medications too.

The workers are also concerned about a bed shortage at psychiatric hospitals, where the number of beds is already limited due to their high cost.

There aren’t designated COVID-19 floors at state psychiatric hospitals, and given the open layout, where beds sit next to one another, there’s an opportunity for the virus to spread readily between patients.

“If you have an infection happening in the unit, it’s going to spread super rapidly,” Mitsuishi said. “If we start to lose units at state hospitals [to COVID-19], then it’s going to be really scary.”

ReportsTrusted Source have shown that respiratory infections, including the flu, account for the most outbreaks in psychiatric units.

COVID-19, which is thought to be more contagious than influenza, could strike these places just as hard.

Preparing and gathering resources takes time. Psychiatric units and mental health clinics need to act quickly to ensure they have a plan in place when an outbreak strikes.

“It’s all about timing, right,” Mitsuishi said. “We are flattening the curve so we can prepare for as long as possible of a surge [due to the coronavirus].”

EXHIBIT 7

VIEWPOINT

Addressing the COVID-19 Pandemic in Populations With Serious Mental Illness

Benjamin G. Druss, MD, MPH
Rollins School of Public Health, Emory University, Atlanta, Georgia.

The coronavirus disease 2019 (COVID-19) pandemic will present an unprecedented stressor to patients and health care systems across the globe. Because there is currently no vaccine or treatment for the underlying infection, current health efforts are focused on providing prevention and screening, maintaining continuity of treatment for other chronic conditions, and ensuring access to appropriately intensive services for those with the most severe symptoms.[1]

Disasters disproportionately affect poor and vulnerable populations, and patients with serious mental illness may be among the hardest hit. High rates of smoking in this population may raise the risk of infection and confer a worse prognosis among those who develop the illness.[2] Residential instability and homelessness can raise the risk of infection and make it harder to identify, follow up, and treat those who are infected.[3] Individuals with serious mental illnesses who are employed may have challenges taking time off from work and may lack sufficient insurance coverage to cover testing or treatment. Small social networks may limit opportunities to obtain support from friends and family members should individuals with serious mental illness become ill. Taken together, these factors may lead to elevated infection rates and worse prognoses in this population.

What strategies are available to mitigate the outcome of this epidemic among patients with serious mental illness? Federal preparedness policies developed in the wake of complex disasters have increasingly embraced the notion of whole community preparedness, which supports building and supporting structures at multiple levels to prepare and respond, particularly for vulnerable populations.[4] Within the public mental health care system, this includes engagement with mental health service users, clinicians, and federal and state policies.

Supporting Patients With Serious Mental Illness

People with serious mental illnesses should be provided with up-to-date, accurate information about strategies for mitigating risk and knowing when to seek medical treatment for COVID-19. Patient-facing materials developed for general populations will need to be tailored to address limited health literacy and challenges in implementing physical distancing recommendations because of poverty and unstable living situations. Messaging will need to provide assurances that those who seek care will not face penalties with regards to cost or immigration status. Patients will need support in maintaining healthy habits, including diet and physical activity, as well as self-management of chronic mental and physical health conditions.

It will also be important to address the psychological and social dimensions of this epidemic for patients. Worry could both exacerbate and be exacerbated by existing anxiety and depressive symptoms. Physical distancing strategies critical for mitigating the spread of disease may also increase the risk of loneliness and isolation in this population. Those who become ill may face dual stigma associated with their infections and their mental health conditions. For any given patient, psychological symptoms will emerge in a unique personal and social context that should be considered in developing a treatment plan.

Empowering Mental Health Clinicians

Mental health clinicians are often the primary point of contact with the broader health care system for their patients with serious mental illnesses, and as such will represent the first responders to the COVID-19 pandemic for many of these individuals. Mental health clinicians need training to recognize the signs and symptoms of this illness and develop knowledge about basic strategies to mitigate the spread of disease for both in their patients and themselves. Clinicians should have discussions with their patients about how best to implement the strategies.

Clinicians will need support in maintaining their own safety and well-being. Where possible, services should be delivered via telehealth rather than in person, and when in-person visits are necessary, in individual rather than group formats. Child and elder care should be made available for mental health clinicians working extra shifts. Support from colleagues will be essential for maintaining physical, mental, and social well-being, particularly if the pandemic is of an extended duration.

Strengthening Mental Health Care Systems

The COVID-19 pandemic is likely to place a major strain on community mental health centers and state psychiatric hospitals. These facilities have limited capacity to screen for or treat medical conditions, and few have existing relationships with local or state public health agencies. It is critical for these organizations to develop continuity-of-operations plans to ensure that they can maintain vital functions in the face of staff illnesses or shortages of psychotropic medications. Clinics will need protocols for identifying and referring patients at risk for infection and self-quarantine strategies for clinicians who develop symptoms of the illness. Adequate environmental protections including well-ventilated spaces, easy access to handwashing, and personal protective equipment should be available. Institutional settings, including state psychiatric hospitals, nursing homes, and long-term care facilities, will be at particularly high risk for

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outbreaks and need to ensure that they have contingency plans to detect and contain them if they occur.

Expanding Mental Health Policies

The coming weeks will see a wave of new federal legislation and regulations and state policies developed to mitigate the health and economic outcomes of the COVID-19 outbreak.[5] These policies will have particular urgency for populations with serious mental illness because of their elevated risks. State mental health authorities will play a critical role in creating and administering policies regarding COVID-19 in their state hospitals and community mental health clinics. The role of social policies, such as the Supplemental Nutrition Assistance Program, housing support, and paid sick leave for hourly employees will be vital for ensuring the health and well-being of this population.

The COVID-19 pandemic will create unprecedented health and social challenges both in the US and internationally. People with serious mental illnesses will be at uniquely high risk during this period, as will be the public mental health care system central to delivering their care. Careful planning and execution at multiple levels will be essential for minimizing the adverse outcomes of this pandemic for this vulnerable population.

ARTICLE INFORMATION

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EXHIBIT 8

urgently needed. China's endeavours to foster medical humanities education reforms should be actively promoted at the level of research, policy, and practice.

We declare no competing interests.

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COVID-19 testing and patients in mental health facilities


Science Photo Library

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People residing in psychiatric treatment facilities are at high risk for coronavirus disease 2019 (COVID-19). Given the absence of a vaccine or treatment, prevention is the primary guard against adverse events, such as acute respiratory distress syndrome and death. However, prevention requires keeping infected and uninfected patients apart as much as possible.

Because some patients with COVID-19 can be contagious yet asymptomatic, especially in the initial days after infection, knowing who is infected requires timely diagnostic testing as well as when and how a patient was exposed and when symptoms began. This could be challenging in individuals with psychiatric or substance use disorders as some are unable to recall or are unaware of potential exposures and symptom onset.

Even under optimal conditions, current diagnostic tests do not effectively identify infected individuals and, as more people become infected, the number of false negatives increases. Furthermore, new polymerase chain reaction and serological tests arise each week, often with limited performance information, which adds to the confusion about COVID-19 tests.[1]

People with psychiatric conditions or substance use disorders, particularly those in residential treatment or inpatient facilities, are at increased risk of exposure to COVID-19, not only because of the difficulty in evaluating their medical symptoms and history, but also because of frequent patient turnover, limited space and staff, and general resource constraints in many facilities. Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the virus responsible for the development of COVID-19—pose a substantial threat of spreading the virus because they come in contact with other susceptible individuals given the close quarters and communal living environments. Furthermore, these patients are at higher risk for complications of COVID-19 because they frequently have underlying medical conditions that worsen their prognosis (eg, cardiac disease, history of smoking).

The vulnerability of institutionalised populations has been noted by clinicians and researchers, and we extend this work by drawing attention to this particularly high-risk subgroup and the problems posed by the performance of current diagnostic technology.[2,3]

One solution would be to test all individuals for COVID-19 before entry into treatment facilities. Testing capacity has improved; however, access remains limited and test sensitivity is modest, which results in false negatives.[4,5] Test performance is further compromised by variations in test quality, sample collection, and duration of symptom onset, increasing the potential for error.[6] For example, for a patient presenting with disorganised thinking or altered mental status, determining the date of onset of non-specific symptoms such as a cough might be difficult. Thus, the pretest probability of infection with SARS-CoV-2 could be

hard to estimate. Fundamentally, when the sensitivity of a test is limited and the disease course for a patient is unknown, the test outcome could be unreliable and infectious patients could be placed erroneously in treatment facilities.

Already, there has been evidence of rapid spread of COVID-19 through long-term care facilities and inpatient psychiatry units,[7,8] with several reporting patient deaths attributed to COVID-19. Non-pharmacological interventions such as physical distancing and frequent handwashing can be difficult to implement in these types of inpatient or residential settings, as some individuals might not be able to adhere to recommendations.

Best practice should involve screening all patients for symptoms of COVID-19, particularly before admission, and a protocol should be implemented for management of inpatients who develop symptoms.[9]

One potential strategy for improving detection could involve testing all patients for COVID-19 at two or more time points before entry to the inpatient unit to mitigate the risk of false negative results for those with uncertain time of disease onset. Another would be to require sample testing from multiple body sites with more than one sample, analogous to blood culture protocols, which could address concerns about sampling technique. Patients infected with SARS-CoV-2 should remain separated from other people until testing indicates they are no longer infectious.

As serological tests and additional diagnostic or risk information become available, diagnostic certainty and detection should improve, at which point existing protocols should be adapted. Because of the potential for rapid spread and serious complications, implementation of such preventative efforts must occur immediately. This should be done in combination with the development of a rigorous evidence base monitoring diagnostic testing and disease transmission in this rapidly changing environment by use of creative study designs.

In addition to testing patients, prevention should centre around providing safe conditions for patients and staff. The United States Centers for Medicare and Medicaid Services recently released guidelines allowing for patient separation on the basis of COVID-19 status for patients in long-term care facilities.[10] Analogous considerations for individuals with mental illness in residential or acute care facilities would probably benefit this population.

These recommendations are burdensome, but necessary given increasing reports of rapid spread within facilities housing susceptible individuals. The structure of these facilities and patient populations make monitoring illness course and preventing the spread of COVID-19 more difficult, but these risks can be mitigated by employing testing strategies that attempt to lift the shroud of false negative test results.

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EXHIBIT 9

Psychosocial Interventions to Reduce Premature Mortality in Patients With Serious Mental Illness

The mortality rate is unacceptably high in patient with serious mental illnesses. Several psychosocial interventions have been developed that may benefit these patients.

TABLE. Factors associated with the higher mortality rates in patients with severe mental disorders[16]

• Factors related to the disorder itself (due to decline in cognitive functioning, and tendency to avoid routine check-up visits and neglect of physical health)
• Factors related to pharmacological treatments (eg, metabolic adverse effects of antipsychotic medications)
• Factors related to the organization of mental health system and attitudes of health professionals (due to lack of parity between physical and mental health services)
• Factors related to patients' unhealthy lifestyle behaviors (ie, inactivity, poor diet, use of psychoactive substances, altered circadian rhythms, smoking)

SPECIAL REPORT: ADDRESSING MORTALITY

Compared with the general population, patients with serious mental illness (SMI), ie, schizophrenia, major depression, and bipolar disorders, have higher levels of morbidity, poorer health outcomes, and higher mortality rates.[1] In particular, life expectancy is reduced up to 25 years.[2] The causes of this premature mortality have been extensively analyzed, and the vast majority is due to the higher incidence of physical health problems, such as cancer as well as cardiovascular, respiratory, metabolic, and infectious diseases.[3,4] The higher mortality rates are due to different factors, which are summarized in the **Table**.

This mortality gap between the general population and people with SMI is considered a "public health scandal."[5] Hence, several international organizations have advocated for individual and community-based interventions to reduce mortality in these patients. In particular, the World Health Organization has recently developed international guidelines on how to improve physical health in people with severe psychiatric disorders and has provided a set of actions to be undertaken by national health systems, including

control of risk factors, scaling up management in primary health care, and development of national policies.[6] According to WHO, since the premature mortality is a complex phenomenon resulting by the interaction of several protective and risk factors, a single approach is likely to be inadequate. A multilevel approach would be more appropriate for the long-term management of physical and mental health conditions.

The role of psychosocial interventions for improving lifestyle behaviors

Several psychosocial interventions, including behavioral, educational, and psychological components, have been developed worldwide in order to improve lifestyle behaviors in patients with SMIs.[7] These approaches, if proved to be effective, would have to be disseminated on a large scale.

Recently developed in Denmark, CHANGE is an intervention that targets physical inactivity, unhealthy dietary habits, and smoking, and is facilitates contact to the general practitioner.[8] It is based on the theory of stage of change, motivational interviewing, and an assertive approach adapted from the assertive community treatment. The three methods were incorporated in four manuals with detailed descriptions of the intervention addressing care-coordination, smoking cessation, healthy diet, and increased physical activity. The intervention is led by a coach, who supports the patient in setting up individual goals and paying attention to his or her priorities, values, and life conditions. The coaches are available for short message services, phone calls, or home visits, as needed. They are health professionals (eg, occupational therapists, physiotherapists, dieticians) with clinical training in psychiatry. Findings from the CHANGE trial indicate that intervention was effective in reducing the mean age-standardized 10-year cardiovascular risk.[8,9]

In the US, Green and colleagues,[10] have developed the STRIDE intervention, which is a 12-month intervention consisting of three phases:
1. An intensive phase of weekly group sessions for 6 months covering information on nutrition, physical activity, and lifestyle changes
2. A maintenance intervention phase, covering the same areas of previous phase through problem solving and motivational enhancement
3. Individual monthly contacts for the remaining 6 months of the intervention
Using a manualized protocol, participants are asked to implement a series of specific strategies for achieving changes in behavior, activity level, and weight. In particular, participants are encouraged to routinely monitor food intake, calories, and physical activity, to set reasonable short-term goals, to formulate specific plans, and to develop social support. Manuals are available for download and can be easily used in clinical care. Patients who received the STRIDE intervention reported significant weight reduction.

The SHAPE program was developed for obese people with SMIs.[11] The intervention includes gym membership, weekly individual meetings with a certified fitness trainer, and information on healthy eating. A motivational component is also included in the program, coupled with a specific focus on the management of psychiatric symptoms that can interfere with exercise and healthy eating. A significant BMI reduction was seen in the patients who took part in the program.

MOVE! is a weight management program developed by the Veterans Health Administration, which has been manualized in order to address the needs of veterans with serious mental illness.[12] MOVE! is a 6-month weight management approach that includes psychoeducation as well as behavioral and motivational strategies that focus on nutritional counselling, caloric expenditure, and portion control. During the sessions, visual aids are used. Although results from MOVE! participants did not differ from those of the control group, this program has been adapted to be provided through 30 Internet-based interactive educational modules (WebMOVE).[13] Compared with patients who received the in-person intervention, those who received the WebMOVE intervention reported a more significant weight loss-highlighting the possible role of the Internet for these programs.

We have recently developed the LYFESTYLE intervention, a new psychosocial approach that aims to improve physical health in people with SMI.[14] It is a 5-month group intervention that includes elements taken from psychoeducation, cognitive-behavioral therapy, and motivational interview. At each session, participants are provided with booklets, homework, and daily diaries to keep track of any changes. The sessions end with a 20-minute moderate physical activity. The primary outcome is a reduction of BMI and an improvement on the Framingham and HOMA indexes at the end of the intervention. At 2 years of follow up, these outcome measures are expected to increase and can be considered as an indirect measure of mortality preventionThe multicentric randomized controlled trial that compared the LIFESTYLE intervention with a control informative intervention included 402 patients.

A collection of the most promising psychosocial interventions to improve lifestyle behaviors in people with SMIs was recently published.[15] All available psychosocial interventions differ in the target population (individuals or groups; diagnostically closed or open

to different categories of patients); the inclusion of different psychosocial components in the intervention (eg, motivational, educational, problem-solving, self-help); the type of health professionals involved (eg, psychiatrists, psychologists, nurses, dieticians, personal trainers); the duration of the intervention and the provision of booster sessions.

It is not clear which format yields the best results. In fact, while the individual format prioritizes the motivational component and allows treatment personalization based on the needs of each participant, the group format allows patients to share their experiences and to provide reciprocal support.

Another important consideration is the involvement of a multidisciplinary team. When the intervention is provided by mental health professionals only, its long-term efficacy is low. It is likely that specific components of the interventions (ie, those related to physical activities or diet habits) can be more easily changed by involving professionals with specific knowledge and training. Of course, the cost-to-benefit ratio should always be considered, in particular the costs related to the recruitment of professionals different from those already working in mental health.

Many trials have included a motivational component, which represents the core active ingredient for most psychosocial interventions that aim to improve lifestyle behaviors in patients with SMI. The target of the different proposed approaches varies significantly; in some cases, interventions are focused on diet and healthy food, while in other cases different aspects of lifestyle behaviors (such as smoking, regular physical activity, sleep hygiene) are prioritized. Moreover, the duration of the intervention is very heterogeneous. Some interventions last 3 months, while others can last up to 2 years. With longer interventions, the most relevant difficulties are related to the high rate of patient drop-outs and the excessive workload for clinicians who are involved in the intervention. However, the “minimum effective dosage” is not yet clear.

Conclusions

Psychosocial interventions that target lifestyle behaviors represent a promising approach for challenging the premature mortality in patients with SMI. However, their use in clinical practice is rare and preventive strategies that can be easily integrated in routine care should be adopted. In particular, clinicians should regularly check lifestyle behaviors of their patients and provide them with adequate information on the positive effects of healthy diet, physical activity, and smoking cessation. Specific training on these aspects should be included in educational curricula for residents and trainees, with a particular focus on motivational interviewing, psychoeducation, and problem-solving. An ideal approach should not be too long and should be conducted by trained mental health clinicians in conjunction with other health professionals. The group format seems to be the best option, as it reduces the costs and increases patients’ motivation. There is still a long way to go, but at least now the way is tracked.

Disclosures:

Dr Fiorillo *is Full Professor, and* **Dr Sampogna** *and* **Dr Luciano** *are Assistant Professors, Department of Psychiatry, University of Campania “L. Vanvitelli,” Naples, Italy.* *The authors report no conflicts of interest concerning the subject matter of this article.*

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EXHIBIT 10

The Coronavirus Crisis

COVID-19 Infections And Deaths Are Higher Among Those With Intellectual Disabilities

June 9, 2020 · 5:00 AM ET
Heard on Morning Edition

JOSEPH SHAPIRO

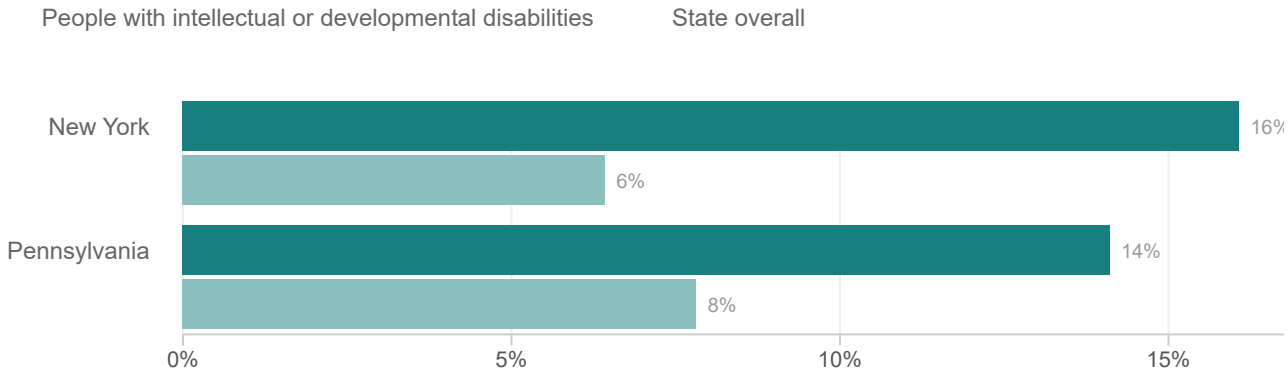
4-Minute Listen

PLAYLIST Download

Transcript

People With Intellectual Disabilities And Autism Die Of COVID-19 At A Higher Rate

In New York and Pennsylvania, COVID-19 case-fatality rates for people with intellectual and developmental disabilities are higher than the states' overall rates. (Case-fatality rates are deaths as a percentage of total confirmed cases within the population.)



Notes

Data as of June 3. Numbers for people with intellectual disabilities reflect those who get services from the state.

Source: New York State Department of Health, Pennsylvania Department of Health, Pennsylvania Office for People with Developmental Disabilities, New York Office for People with Developmental Disabilities

Credit: Stephanie Adeline/NPR

People with intellectual disabilities and autism who contract COVID-19 die at higher rates than the rest of the population, according to an analysis by NPR of numbers obtained from two states that collect data. They also contract the virus at a higher rate, according to research looking into group homes across the United States.

In Pennsylvania, numbers obtained by NPR show that people with intellectual disabilities and autism who test positive for COVID-19 die at a rate about twice as high as other Pennsylvania residents who contract the illness.

In New York, the state with the most deaths from COVID-19, people with developmental disabilities die at a rate 2.5 times the rate of others who contract the virus.

The numbers in Pennsylvania are compiled by the Office of Developmental Programs of the Pennsylvania Department of Human Services and count people who get state services while living in group homes, state institutions or in their own homes. As of June 2, there were 801 confirmed cases and 113 deaths among people with intellectual disabilities and autism. In New York, NPR calculated data obtained from the New York State Office for People with Developmental Disabilities. Of people who get state services from that office, 2,289 have tested positive for COVID-19 and 368 have died.

The high rate of death "is disturbing, but it's not surprising," says Scott Landes, an associate professor of sociology at Syracuse University's Maxwell School of Citizenship and Public Affairs.

He's been collecting his own data from state and private research groups and says people with developmental disabilities who live in group homes have some of the highest death rates from COVID-19 in the country.

"They're more likely — four times more likely, we're showing — to actually contract COVID-19 than the general population," he says. "And then if they do contract COVID-19, what we're seeing is they're about two times more likely to die from it."

That's higher than the death rates for Hispanics and African Americans.

Landes co-authored a recent study that used private health records to show that 18- to 74-year-olds with developmental disabilities, mostly those diagnosed with autism, who contracted COVID-19 died at nearly twice the rate as others.

THE CORONAVIRUS CRISIS

Hospital Visitor Bans Under Scrutiny After Disability Groups Raise Concerns Over Care

THE CORONAVIRUS CRISIS

In New York Nursing Homes, Death Comes To Facilities With More People Of Color

Landes says there are two reasons for the high death rates. People with developmental disabilities are far more likely to have a preexisting health condition, such as respiratory disease, that adds to their risk. They're much more likely, than even elderly people, to live in a setting with roommates and staff like group homes where two or four or 10 or more people live together. About 13% to 20% of people with developmental disabilities live in such settings, Landes notes, compared with only about 6% of people over age 65.

"You reside with multiple roommates, with staff coming in and out," says Landes, "your chances of actually contracting COVID are high. And then if someone in your home gets it, it's like there's nowhere you can go."

There has been a lot of attention to the deaths in nursing homes, and with good reason. About a third of all deaths nationwide from COVID-19 have been linked to them. According to the federal Centers for Medicare & Medicaid Services, there have been at least 31,782 deaths of nursing home residents from COVID-19 as of May 31. The CMS total does not count nursing home staff who died.

Medics suit up in personal protective equipment as they prepare to pick up a patient in severe respiratory distress from a group home in the Borough Park neighborhood of Brooklyn on May 11.

Spencer Platt/Getty Images

Still, says Nicole Jorwic, senior director for public policy at the Arc, a group that represents people with intellectual and developmental disabilities, there are consequences to paying less attention to people who live in other care home settings.

One result, she says, is that it has been harder for the groups that serve people with disabilities to get personal protective equipment or extra pay for staff workers. In most states, these workers don't get the bonus pay that is sometimes offered to other front-line health care workers and, in some states, the staff who serve people in group homes or their own homes aren't considered essential workers.

"You don't go into a hospital and some doctors have on masks and some don't. Or some are underpaid and some are not," says Antonio McCall, a direct service provider who works with two men at a Philadelphia group home. "No, everyone gets what they're working for. Everyone's covered with protection, because that's what's required."

There have been no infections at the house where McCall works, but there have been some outbreaks of COVID-19 — and even a death — at others. He says his agency managed to find masks for him, and he has received some extra pay.

And McCall is careful. He doesn't want to bring an infection into the group home or his own home, where he helps care for his mother, who has an underlying health condition, and is raising his niece and nephew.

In New York, a direct service professional working in a group home makes little money — "at or below the poverty line," in the mid $20,000s a year, says Tom McAlvanah, president of New York Disability Advocates, a coalition of service providers. He says it has been hard to keep workers healthy and on the job. They're vulnerable not only because of where they work, but because they often rely on public transportation.

McAlvanah says New York's Medicaid program, the main source of payment for group home providers, has failed to increase reimbursements even before the coronavirus pandemic. Now, he says, group home residents have stopped going to work and group home providers have had to pay staff — without government reimbursement — to work more hours and overtime to run the group homes where residents now spend their full days.

That's the case in most states, although Colorado and several others did increase Medicaid resources to providers. The CARES Act, the coronavirus relief act signed into law in March, became a source of extra funding, but only through the end of June.

Provider agencies say that, on average, they've spent a third of their annual revenue on unexpected costs from the pandemic and have cash reserves to cover a month or less of operations, according to a recent national survey by the American Network of Community Options and Resources, a trade association for groups that provide services to people with disabilities.

"For years and years and years, people we serve in group homes like this, they're the forgotten people," says Todd Goodwin, who runs John F. Murphy Homes, a large provider agency in Maine. "Nobody sees them. Nobody notices them. We see that repeatedly through policy, we see that in financing at the state and federal level. It's been an issue for years."

In Washington state, there was a Zoom meeting last month of men and women with developmental disabilities who belong to an advocacy group called People First of Washington. They spoke of their opposition to state budget cuts that, they worried, would cut off public transportation that they depend on to get to work or cut the hours of their state-funded caregivers. And they were worried about the effects of the coronavirus.

Shane Cody Fairweather, who lives in his own apartment in Chewelah, Wash., with support from service providers, said in an interview that he worries that people like him are not getting attention, despite their risks for contracting COVID-19.

"We're part of society. We're more vulnerable," he says. "It should be on equal footing. They should be paying attention to the elderly and the disabled as well."

Fairweather says there have been no outbreaks of the coronavirus in the apartments where he lives. He's healthy and ready to return to his job as a janitor at the local library.

More Stories From NPR

EXHIBIT 11

People With Intellectual And Developmental Disabilities More Likely To Die From Covid-19

Marla Milling Contributor ⓘ

Healthcare

I am a Forbes.com Contributor specializing in geriatric health and women's health articles.

A nurse pulls a suitcase as she helps a patient at Saint-Louis hospital in Paris, on May 28, 2020 as ... [+] AFP VIA GETTY IMAGES

Syracuse University and SUNY Upstate Medical University researchers recently analyzed more than 30,000 people who tested

positive for Covid-19 and found that those with intellectual and developmental disabilities (IDD) are more likely to die that those without IDD.

Breaking the data down by age group shows:

· Ages 0-17 – for every 100 people with Covid-19, 1.6 with IDD died compared to less than one without IDD

· Ages 18-74 – for every 100 people, 4.5 with IDD died; 2.7 without IDD

· Ages 75 and over – for every 100 people, 21.1 with IDD died; 20.7 without

"Based upon the case fatality rates we report among those ages 18-74, if 100,000 individuals with IDD contract Covid-19—which is entirely possible in light of the estimates of the size of this population and the cumulative incidence rates we are seeing in our research—we would expect 4,500 to die," says Scott Landes, associate professor of sociology at Syracuse University.

"Comparatively," he adds, "among 100,000 individuals without IDD, we would expect 2,700 to die. That would be an excess of 1,800 IDD deaths and in my mind that is unacceptable."

While the study did not investigate cause, the researchers noted that people with IDD had a higher prevalence of comorbid circulatory, respiratory and endocrine disease across all age groups.

They also say that there's a higher percentage of people with IDD who live in congregate settings.

"More attention is needed to this vulnerable health population in order to ensure their safety and well-being during this pandemic, including careful attention to the impact of public policies such as PPE (personal protective equipment) prioritization and funding streams on the ability of residential service providers to guarantee quality of care during this time," says Landes.

The study appears in Science Direct's *Disability and Health Journal*.

Follow me on Twitter or LinkedIn. Check out my website or some of my other work here.

Marla Milling

I am a full-time freelance writer in Asheville, North Carolina. I've written more than 900 published articles/essays for a wide variety of publications including...

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EXHIBIT 12

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2.3 MILLION CALIFORNIANS ARE LIVING WITH OR CARING FOR A LOVED ONE WITH ALZHEIMER'S OR DEMENTIA.

24/7 HELPLINE: 800.272.3900

The Alzheimer's Association is here all day, every day for people facing Alzheimer's and all dementia through our free 24/7 Helpline (800.272.3900) and website at alz.org. Support is available in 200 languages.

Coronavirus (COVID-19): Tips for Dementia Caregivers

Most likely, dementia does not increase risk for COVID-19, the respiratory illness caused by the new coronavirus, just like dementia does not increase risk for flu. However, dementia-related behaviors, increased age and common health conditions that often accompany dementia may increase risk.

For example, people with Alzheimer's disease and all other dementia may forget to wash their hands or take other recommended precautions to prevent illness. In addition, diseases like COVID-19 and the flu may worsen cognitive impairment due to dementia.

Tips for dementia caregivers at home

Caregivers of individuals living with Alzheimer's and all other dementia should follow guidelines from the Centers for Disease Control (CDC), and consider the following tips:

- For people living with dementia, increased confusion is often the first symptom of any illness. If a person living with dementia shows rapidly increased confusion, contact your health care provider for advice. Unless the person is having difficulty breathing or a very high fever, it is recommended that you call your health care provider instead of going directly to an emergency room. Your doctor may be able to treat the person without a visit to the hospital.
- People living with dementia may need extra and/or written reminders and support to remember important hygienic practices from one day to the next.
  - Consider placing signs in the bathroom and elsewhere to remind people with dementia to wash their hands with soap for 20 seconds.
  - Demonstrate thorough hand-washing.
  - Alcohol-based hand sanitizer with at least 60% alcohol can be a quick alternative to hand-washing if the person with dementia cannot get to a sink or wash his/her hands easily.
- Ask your pharmacist or doctor about filling prescriptions for a greater number of days to reduce trips to the pharmacy.
- Think ahead and make alternative plans for the person with dementia should adult day care, respite, etc. be modified or cancelled in response to COVID-19.
- Think ahead and make alternative plans for care management if the primary caregiver should become sick.

EXHIBIT 13

Management of physical health conditions in adults with severe mental disorders

WHO GUIDELINES

World Health Organization

Management of physical health conditions in adults with severe mental disorders

WHO GUIDELINES

World Health Organization

Guidelines for the management of physical health conditions in adults with severe mental disorders

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Acronyms & abbreviation

AE	Adverse effect
ARV	Antiretroviral
CBT	Cognitive behaviour therapy
EMBASE	Excerpta Medica Database
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIC	High-income country
LMIC	Low- and middle-income country
MeSH	Medical Subject Headings
MD	Mean difference
MDR-TB	Multi drug resistant tuberculosis
mhGAP	Mental Health Gap Action Programme
NCD	Non-communicable diseases
OR	Odds ratio
PEN	Package of Essential Noncommunicable Disease Interventions
PICO	Population Intervention Comparison Outcome
RCT	Randomized controlled trial
RR	Relative risk
SMD	Severe mental disorders
SMR	Standardized mortality ratio

Executive summary

INTRODUCTION

The global burden of disease due to mental disorders continues to rise, especially in low- and middle-income countries (LMIC). In addition to causing a large proportion of morbidity, mental disorders – especially severe mental disorders (SMD) – are linked with poorer health outcomes and increased mortality. SMD are defined as a group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders. People with SMD have a two to three times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy. While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to physical health conditions, both non-communicable and communicable. Furthermore, people with SMD are more likely to engage in lifestyle behaviours that constitute risk factors for non-communicable diseases (NCDs) such as tobacco consumption, physical inactivity and consuming unhealthy diets.

Most studies reporting the excess mortality in people with SMD are from high income countries. The situation may be much worse in LMIC where the resources are inadequate, the institutions are not well managed and access to quality mental health care and physical care is limited.

Equitable access to comprehensive health services remains out of reach for the majority of people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, including promotion and prevention, screening, and treatment. It is crucial to address the disparities in health care access and provision for people with SMD. Following the principle of non-discrimination and universal health coverage as elaborated in target 3.4 of the United Nations Sustainable Development Goals ("By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote of mental health and well-being"), people with SMD should be offered at least the same level of treatment for physical health conditions and their risk factors as the general population.

The WHO *Comprehensive Mental Health Action Plan (2013-2020)* outlines a vision where people living with mental disorders are able to exercise the full range of human rights and to access high quality, culturally-appropriate health and social care in a timely way to promote recovery. In service of this vision and as part of WHO's Mental Health Gap Action Programme (mhGAP), these *Guidelines on the management of physical health conditions in adults with severe mental disorders* will provide up-to-date, evidence-based recommendations to support the scale-up of care for physical health conditions and their risk factors affecting people living with SMD globally.

Accordingly, the objective of these guidelines is:

To improve the management of physical health conditions in adults with SMD and support the reduction of individual health behaviours constituting risk factors for these illnesses, with the aim of decreasing morbidity and premature mortality amongst people with SMD.

Existing WHO guidelines for the general population are relevant to the physical health conditions that increase the morbidity and mortality for people with SMD. For example, the *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource*

Settings Geneva, WHO, 2010 provides guidelines and recommendations for tobacco cessation, weight management, cardiovascular disease prevention including diabetes management and prevention of complications, treatment and prevention of chronic respiratory diseases in the general population. Other WHO guidelines for infectious disease are also relevant such as the *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations. WHO, 2016 update* and *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. WHO, 2017.*

GUIDELINE DEVELOPMENT METHODS

The process of development of these guidelines followed the *WHO handbook for guideline development* and involved: (1) recruitment of the Guideline Development Group (GDG); (2) declaration of interest by GDG members and peer reviewers; (3) scoping review to formulate questions and select outcomes (4) identification, appraisal and synthesis of available evidence; (5) formulation of recommendations with inputs from a wide range of stakeholders; and (6) preparation of documents and plans for dissemination.

The GDG, an international group of experts, provided input into the scope of the guideline and assisted the steering group in developing the key questions. A total of one background question and seven PICO (Population, Intervention, Comparison, and Outcome) questions were developed.

To address the PICO questions, a series of searches for systematic reviews was conducted and GRADE evidence profiles prepared. During a meeting at WHO headquarters in Geneva, 9 – 10 May 2018, the GDG discussed the evidence, sought clarifications, and interpreted the findings in order to develop recommendations. The GDG considered the relevance of the recommendations for people with SMD including the balance of benefit and harm of each intervention; values and preferences of people with SMD; costs and resource use; and other relevant practical issues for providers in LMIC.

When making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweigh any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. Strong recommendations imply that most individuals would want the intervention and should receive it while conditional recommendations imply that different choices may be appropriate for individual people and they may require assistance at arriving at management decisions. The GDG members reached an unanimous agreement on all the recommendations and ratings.

SUMMARY OF RECOMMENDATIONS

Tobacco cessation

In the context of tobacco cessation programmes:

Recommendation 1:
In people with severe mental disorders, combined pharmacological and non-pharmacological interventions may be considered in accordance with the WHO training package (*Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package*). *(Strength of recommendation: Conditional; quality of evidence: Very low).*

Recommendation 2:
In people with severe mental disorders, a directive and supportive behavioural intervention programme may be considered and should be tailored to the needs of the population. *(Strength of recommendation: Conditional; quality of evidence: Very low).*

Recommendation 3:
In people with severe mental disorders, varenicline, bupropion and nicotine replacement therapy may be considered for tobacco cessation. *(Strength of recommendation: Conditional; quality of evidence: Very low).*

BEST PRACTICE STATEMENT:
Prescribers should take into account potential interactions between buproprion and varenicline with psychotropic medications as well as possible contra-indications.

Weight management

Recommendation 1:
Behavioural lifestyle (healthy diet, physical activity) interventions should be considered in all people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese in accordance with *WHO's Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).* These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Strong; Quality of evidence: Very low).*

Recommendation 2:
For people with severe mental disorders who are overweight or obese, and where lifestyle interventions and/or switching psychotropic medication do not appear successful, adjunctive metformin may be considered. This should be considered under close clinical supervision and monitoring.
(Strength of recommendation: Conditional; Quality of evidence: Low).

BEST PRACTICE STATEMENTS:

- For people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese, initiating a psychotropic medication with lower propensity for weight gain should be considered, taking into account clinical benefits and potential adverse effects.
- For people with severe mental disorders who are overweight or obese, switching to a psychotropic medication with a lower propensity for weight gain may be considered, taking into account clinical benefits and potential adverse effects.

Substance use disorders

Recommendation 1:

For people with severe mental disorders and comorbid substance use disorders (drug and/or alcohol), interventions should be considered in accordance with the WHO mhGAP guidelines. *(Strength of recommendation: Conditional; Quality of the evidence: Low).*

Recommendation 2:

Non-pharmacological interventions (e.g. motivational interviewing) may be considered and tailored to the needs of people with severe mental disorders and substance use disorders *(Strength of recommendation: Conditional; Quality of the evidence: Very low).*

BEST PRACTICE STATEMENT:

Prescribers should take into account the potential for drug-drug interactions between medicines used for treatment of substance use disorders and severe mental disorders.

Cardiovascular disease and cardiovascular risk

Recommendation 1:

For people with severe mental disorders and pre-existing cardiovascular disease, or with cardiovascular risk factors (e.g. high blood pressure or high cholesterol), pharmacological and non-pharmacological interventions may be considered in accordance with the *WHO Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010)* for lowering cardiovascular risk and management of cardiovascular disease.
(Strength of recommendation: Strong; Quality of evidence: High to moderate for different interventions).

Recommendation 2:

For people with severe mental disorders and pre-existing cardiovascular disease, the following is recommended:

a) Behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

b) Collaborative care i.e. a multi-professional approach to patient care with a structured management plan, scheduled patient follow-up, and enhanced inter-professional communication, may be considered for cardiovascular disease management. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

Recommendation 3:

For people with severe mental disorders and cardiovascular risk factors, behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and pre-existing cardiovascular disease:

- Initiating a psychotropic medication with lower propensity for cardiovascular risk is a strategy that should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to a psychotropic medication with lower propensity for cardiovascular risk may be considered, taking into account clinical benefits and potential adverse effects.

For people with severe mental disorders and pre-existing cardiovascular disease or cardiovascular risk factors:

- Prescribers should be aware of potential interactions between prescribed medicines for cardiovascular disease and prescribed psychotropic medications, which may affect cardiovascular risk. Cardiovascular outcomes and risk factors should be monitored and dose adjustment of cardiovascular medicines may be required.

Diabetes mellitus

Recommendation 1:
For people with severe mental disorders and diabetes mellitus, interventions in accordance with the WHO Package of Essential Non-communicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings should be considered for diabetes management.
(Strength of recommendation: Strong; Quality of evidence: Low).

Recommendation 2:
Behavioural lifestyle interventions should be considered for all people with severe mental disorders and diabetes mellitus. These interventions should be appropriate and tailored to the needs of this population.
(Strength of recommendation: Strong; Quality of evidence: Very low).

Recommendation 3:
In people with depression and comorbid diabetes mellitus, cognitive behaviour therapy for treatment of depression may be considered. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and diabetes mellitus:

- Initiating an anti-psychotic medication with lower propensity for producing hyperglycaemia should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to an anti-psychotic medication with lower propensity for producing hyperglycaemia is a strategy that may be considered, taking into account clinical benefits and potential adverse effects.
- Prescribers should be aware of potential interactions between prescribed medicines for diabetes mellitus and prescribed psychotropic medicines, which may affect glycaemic control. Glycaemic control should be monitored and dose adjustment of medicines may be required.

HIV/AIDS

Recommendation 1:
For people with severe mental disorders and HIV/ AIDS, antiretroviral drugs should be considered in accordance with the *WHO Updated recommendations on first-line and second-line antiretroviral regimens. (Strength of the recommendation: Strong; Quality of the evidence: Moderate)*

Recommendation 2:
Additional psychosocial support for treatment adherence should be provided to people with HIV and severe mental disorders in accordance with the *WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. (Strength of the recommendation: Strong; Quality of the evidence: Moderate)*

BEST PRACTICE STATEMENT:
For people with severe mental disorders and HIV/ AIDS, prescribers should take into account the potential for drug-drug interactions between antiretroviral drugs and psychotropic medicines.

Other infectious diseases (Tuberculosis, Hepatitis B/C)

Recommendation 1:
For people with severe mental disorders and TB, pharmacological management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* and the *WHO treatment guidelines for drug-resistant tuberculosis.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 2:
For people with severe mental disorders and TB, non-pharmacological (social, psychological) management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* and the *WHO treatment guidelines for drug-resistant tuberculosis.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 3:
For people with severe mental disorders and hepatitis B, treatment should be considered in accordance with the *WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 4:
For people with severe mental disorders and hepatitis C, treatment should be considered in accordance with the *WHO guidelines for the screening care and treatment of persons with chronic hepatitis C infection.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

BEST PRACTICE STATEMENT:
For people with severe mental disorders and TBand/or Hepatitis B/, prescribers should take into account the potential for drug-drug interactions between TB medicines, medicines for hepatitis B and C with psychotropic medicines.

1. Introduction

1.1 BACKGROUND AND RATIONALE

Worldwide, mental disorders contribute to 7% of the global burden of disease as estimated by disability adjusted life years and this is rising especially in low- and middle- income countries (LMIC) (GBD 2016). In addition to causing a large proportion of morbidity, mental disorders – especially severe mental disorders (SMD) – are linked with poorer health outcomes and increased mortality. SMD are defined as a group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders. People with SMD have a 2-3 times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy (Liu *et al.*, 2017). People with bipolar disorder and schizophrenia have been shown to have higher rates of mortality in both high and low-income settings (Tsuang, Woolson and Fleming, 1980) (Capasso *et al.*, 2008) (Laursen, 2011) (Nielsen *et al.*, 2013) (Fekadu *et al.*, 2015). One prospective cohort-study in Ethiopia found the overall standardized mortality ratio (SMR) of people with SMD to be twice that of the general population, with schizophrenia associated with the highest risk (SMR three times that of the general population) (Fekadu *et al.*, 2015). Moreover, for schizophrenia in particular, the mortality gap appears to be widening over time (Saha, Chant and McGrath, 2007).

Numerous potential causes have been proposed for the increased mortality of people with SMD, including the well-known evidence-based bidirectional relationship between mental disorders and other non-communicable diseases (NCDs) such as cardiovascular disease, diabetes, respiratory illnesses, and cancers; differential exposure to risk factors driving the aforementioned NCDs such as smoking, harmful use of alcohol, and sedentary behaviour; iatrogenic effects of medications for SMD; and inequitable access to health care services. While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to physical health conditions, both non-communicable and communicable (Liu *et al.*, 2017). Cardiovascular disease, for example, confers a ten-fold higher risk of death than suicide in people with SMD. Overall, people with SMD have approximately 1.5-3 times higher risk of cardiovascular morbidity and mortality when compared with the general population (Correll *et al.*, 2017). People with SMD also have higher rates of diabetes mellitus (Vancampfort *et al.*, 2016), with reports of a 2-3 fold higher prevalence compared with the general population. Infectious diseases such as HIV/AIDS also contribute to the high rates of premature death amongst people with SMD, as do other infectious diseases such as tuberculosis and hepatitis B and C (Saha, Chant and McGrath, 2007).

The figures mentioned above are chiefly drawn from studies from high income countries where health literacy is higher, better quality services are available, and there is overall better monitoring of the institutions and more regular check-ups for physical health of people with SMD. The situation may be much worse in LMICs where the resources are inadequate, the institutions are not well managed and access to quality mental health care and physical care is limited.

SMD can affect and in turn, can be affected by NCDs. People with SMD are also more likely to engage in lifestyle behaviours that constitute risk factors for NCDs. Tobacco consumption (Lasser *et al.*, 2000) is common amongst people with SMD and has been identified as a leading preventable cause of premature mortality in this population. Additionally, people with SMD are more likely to be physically inactive and consume unhealthy diets (Jakobsen *et al.*, 2018), increasing their risk of being overweight or obese. In routine clinical practice, however, such comorbidities and interactions are often overlooked.

Iatrogenic effects of psychotropic medications that are used to treat the symptoms of SMD including antipsychotic medication (and to some extent, antidepressants and mood stabilizers) are also associated with an increased risk of developing physical health conditions and associated complications (Correll *et al.*, 2015) (Correll *et al.*, 2017).

Furthermore, equitable access to comprehensive health services remains out of reach for many people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, including promotion and prevention, screening, and treatment (De Hert *et al.*, 2011). The socioeconomic disadvantages not least due to the stigma and discrimination associated with SMD may further influence affected people's health and health care (Lund *et al.*, 2013). In addition, although families and other informal carers may provide vital practical help to deal with complex comorbidities and navigate health systems, they can be left to struggle under intense stress and with little support themselves (Poon *et al.*, 2017). It is therefore crucial to address the disparities in health care access and provision for people with SMD.

Following the principle of non-discrimination and universal health coverage as elaborated in target 3.4 of the United Nations Sustainable Development Goals ("By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promotion of mental health and well-being"), people with SMD should be offered at least the same level of treatment for physical health conditions and their risk factors as the general population. In some instances, as these guidelines will elaborate further, treatment recommendations for the general population need to be adapted for people with SMD. The benefits and risks of pharmacological interventions need to be balanced against the potential side effects and drug-drug interactions commonly used for SMD. People with SMD often experience impairment in functioning which makes it difficult for them to take the initiative to access health care, to keep appointments or to take medications for physical health conditions as prescribed. Non-pharmacological interventions need to be tailored according to the cognitive, motivational and socio-cultural needs of people with SMD.

Recognizing the frequent comorbidity between mental and physical health conditions, specific recommendations addressing the physical conditions causing the increased morbidity and mortality of people with SMD are needed. These new WHO guidelines constitute an important step in providing better health care for people with SMD, and offer up-to-date, evidence-based recommendations for the management of these physical health conditions and reduction of their risk factors for people with SMD. While these guidelines do not include a comprehensive list of physical health conditions, but have rather focused on those that seemed most important and for which there was evidence available, the physical health conditions (and their risk factors) addressed are those that have been shown to increase morbidity and mortality in people with SMD. It is hoped that these guidelines will benefit people with SMD whose physical health may currently be neglected and may contribute to reduced premature mortality amongst this population.

These guidelines will help achieve the United Nations Sustainable Development Goals 3.4, and facilitate the implementation of *WHO's Comprehensive Mental Health Action Plan* (World Health Organization, 2013). The guidelines build upon prior work by WHO Headquarters and Regional Offices. The WHO Regional Office for Europe published a technical report titled, *Addressing comorbidity between mental disorders and major noncommunicable diseases*, to support implementation of the *WHO European Mental Health Action Plan 2013-2020* and the *WHO European Action Plan for the Prevention and Control of Noncommunicable Diseases 2016-2025* (World Health Organization Regional Office for Europe, 2016). Additionally, the WHO Department of Mental Health and Substance Use Disorder held a consultation on excess mortality in people with SMD with key international experts in December 2015 (World Health Organization, 2015). This consultation included discussions on physical health conditions and the risk factors responsible for excess mortality in this population and the need for evidence-based guidance was recognized.

1.2 RELATED WHO GUIDELINES AND TOOLS

Several existing WHO guidelines and tools designed for the general population are relevant for addressing the physical health conditions and their risk factors causing the increased morbidity and mortality of people with SMD. These were consulted in the guideline development process (Box 1); recommendations were either added or modified for this special population, using targeted evidence reviews and expert opinions to assess the applicability of data for the general population to people with SMD.

1.3 TARGET AUDIENCE

These guidelines are primarily intended for use by health care workers providing services for people with SMD at all levels of the health care system, including outpatient and inpatient care at first-level, second-level, district and tertiary healthcare facilities. Health care providers may include primary care doctors, nurses, specialists, or other members of the health care work force.

In addition, these guidelines are of interest to the following audiences:

- Policy makers and health care planners at the national and local levels
- National and regional mental health programme managers
- National and regional primary care programme managers
- Members of national and local health departments
- People living with SMD and their families
- Groups representing people with SMD and their families

BOX 1: Related WHO guidelines and tools:

1. *Mental Health Gap Action Programme (mhGAP) Intervention Guide for mental, neurological, and substance use disorders in non-specialized health settings (Version 2.0). Geneva, WHO, 2016.* http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/
2. *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings. Geneva, WHO, 2010.* http://www.who.int/cardiovascular_diseases/publications/pen2010/en/
3. *Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package.* http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/
4. *Global recommendations on physical activity for health. Geneva, WHO, 2010.* http://www.who.int/dietphysicalactivity/publications/9789241599979/en/
5. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations. Geneva, WHO, 2016 update.* http://www.who.int/hiv/pub/guidelines/keypopulations-2016/en/
6. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.Recommendations for a public health approach. Second edition. Geneva, WHO, 2016.* http://www.who.int/hiv/pub/arv/arv-2016/en/
7. *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* (http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)
8. *WHO treatment guidelines for drug-resistant tuberculosis* (http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1).
9. *Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. Geneva, WHO, 2015.* http://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/
10. *Guidelines for the screening, care, and treatment of persons with chronic hepatitis C infection. Geneva, WHO, 2016.* http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

1.4
GOAL AND OBJECTIVE

The *WHO Comprehensive Mental Health Action Plan* (2013-2020) outlines a vision where persons living with mental disorders are able to exercise the full range of human rights and to access high quality, culturally-appropriate health and social care in a timely way to promote recovery (World Health Organization, 2013). In service of this vision and as part of *WHO's Mental Health Gap Action Programme (mhGAP)*, these guidelines provide up-to-date, evidence-based recommendations to support improved access to quality care for physical health conditions and to address the risk factors affecting people living with SMD globally. They will be consistent with services oriented towards recovery and focus on the strengths of people with SMD. Accordingly, the objective of these guidelines is:

- To improve the management of physical health conditions in adults with SMD and support the reduction of individual health behaviours constituting risk factors for these illnesses, with the aim of decreasing morbidity and premature mortality amongst people with SMD.

1.5
GUIDING PRINCIPLES

The following principles have informed the development of these guidelines and should guide the implementation of their recommendations:

- The guidelines should expedite the achievement of the goals outlined in the *Mental Health Action Plan (2013-2020)*(World Health Organization, 2013), as well as Goal 3.4 of the Sustainable Development Goals, which focuses on reducing the premature mortality from non-communicable diseases and the promotion of mental health and well-being (United Nations, 2016).

- The process of developing these guidelines and subsequent implementation of recommendations should further the realization of the right to equal levels of health for people living with SMD and promote their active involvement.

- The recommendations should be implemented with accompanying efforts to safeguard the human rights of persons living with SMD, including reduction of stigma, reducing barriers to seeking health services, and ensuring informed decision-making in treatment choices.

Implementation of the recommendations should be informed by the local context, including the availability of financial and human resources. However, the inequities addressed in these guidelines are common across all countries, and should be made a priority in health services.

2. Guideline development process

The *WHO handbook for guideline development*, 2nd edition (http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf) describes the process used in the development of these guidelines, following the steps below.

2.1 GUIDELINE DEVELOPMENT GROUP

A WHO guideline steering group, led by the Department of Mental Health and Substance Use Disorder, was established with representatives from WHO regional offices and relevant WHO departments and programmes. The guideline steering group provided overall support to the guideline development process. Two additional groups were established: a guideline development group (GDG) and an external review group. The GDG included a panel of academics and clinicians with multidisciplinary expertise on the conditions covered by the guidelines. Consideration was given to geographic diversity and gender balance (see Annex 1).

Potential members of the GDG were selected on the basis of their contribution to the area, as well as the need for regional and area of expertise diversity. As a respected researcher in the field, the Chairperson was selected for his extensive experience of guideline development methodology, and his participation in other guideline development groups. Each potential GDG member was asked to complete the WHO declaration of interest (DOI) form. These were reviewed by the steering group.

2.2 DECLARATIONS OF INTEREST AND MANAGEMENT OF CONFLICTS OF INTEREST

All GDG members, peer reviewers and systematic review team members were requested to complete the declaration of interest (DoI) form prior to the evidence review process for guideline development. Invitations to participate in the GDG meeting were sent only after the DoI had been reviewed and approved. The GDG members were also required to complete a confidentiality undertaking. Once received, the WHO Secretariat reviewed the DoIs as well as additional information (internet and bibliographic database search) and evaluated if there are any conflicts of interest and if so, whether these require a management plan. The group composition was finalized after this process.

In order to enhance its management of conflicts of interest as well as strengthen public trust and transparency in connection with WHO meetings and activities involving the provision of technical/normative advice, the names and brief biographies of members being considered for participation in the GDG were disclosed for public notice and comment prior to the meeting.

At the beginning of the GDG meeting, the DoI of each GDG member was presented and GDG members and external partners were asked to update their DoI with relevant changes by notifying the WHO Secretariat.

DoI were reassessed for potential conflict before the face-to-face meeting in Geneva. None of the members had major conflicts of interest. All decisions were documented (see Annex 2).

2.3 COLLABORATION WITH EXTERNAL PARTNERS

The Centre for Global Mental Health, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK (WHO Collaborating Centre for Research and Training in Neurosciences) supported the development of the guidelines by conducting the evidence review and synthesis.

2.4 IDENTIFYING, APPRAISING AND SYNTHESIZING AVAILABLE EVIDENCE

A scoping review helped to identify the key questions that would establish the focus of the recommendations and consisted of the following steps:

1) Initial broad focus on identification of risk factors for excess mortality and morbidity in people with SMD and specific interventions, guided by previous work by the WHO that has highlighted a number of physical health conditions and associated risk factors as critical factors in the excess mortality and morbidity in people with SMD;

2) Review of existing WHO guidelines;

3) Findings of the WHO consultation on the above topic and other relevant WHO documents and discussions with WHO steering group.

A total of one background question and seven key questions in PICO (Population, Intervention, Comparison, and Outcome) format were developed (Annex 3).

The background question provided the context and rationale for the guidelines and addressed the association of physical health conditions with SMD. It consisted of two sub-questions: *What is the comorbidity between physical health conditions (NCDs and infectious diseases) and SMD? What is the impact of physical health conditions on the morbidity and mortality of people with SMD?* The answer to this question was found in a wide range of information sources and summarised the growing body of evidence that has demonstrated the bi-directional relationships between SMD and physical health conditions. The evidence supporting the background question is presented in Annex 4.

Outcomes were rated by GDG members according to their importance as 'critical' for a decision, 'important' or 'unimportant'. Those outcomes rated as critical and important were selected for inclusion into the PICO questions. Regular communication and discussions with the GDG were held by email and teleconferences, respectively.

The WHO steering group, in consultation with the guideline methodologist and GDG chair, proposed a framework based on the PICO questions to review the evidence. The process entailed the following steps: (i) review of evidence that exists for the interventions to manage physical health conditions in people with SMD; (ii) examination of the extent to which existing recommendations for the general population (especially from existing WHO guidelines) can be applied to people with SMD; (iii) examination of when and how these recommendations need to be adapted for people with SMD; and (iv) to provide recommendations that are specific to this population when needed.

The systematic review team developed protocols to review the evidence that existed for the interventions to manage physical health conditions and their risk factors (as outlined in the PICO questions) for people with SMD (Annex 5). Existing relevant systematic reviews were identified for each of the PICO questions. The steering group assessed the quality of existing reviews using the assessment of multiple systematic reviews (AMSTAR) checklist. Systematic reviews found to be of high quality were also assessed for timeliness to ensure that the most current evidence was used. In addition, drug-drug interaction searches were conducted between medicines relevant for each PICO question and medicines used for SMD (Annex 5).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Guyatt *et al.*, 2011) was used to develop the evidence profiles as well as the WHO Handbook for Guideline Development. The quality assessment of the evidence was performed according to GRADE considering study design (randomized controlled trials or observational studies), risk of bias, inconsistency, indirectness, imprecision and risk of reporting bias. Evidence was characterised as either high, moderate, low or very low. The evidence profiles are available at the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html).

2.5 DECISION-MAKING DURING THE GUIDELINE DEVELOPMENT GROUP MEETING

The GDG met at the WHO headquarters in Geneva, 9 – 10 May 2018. The evidence reviews were sent out in advance and summarized in a presentation during the meeting. The GDG members discussed the evidence, clarified points, and interpreted the findings in order to develop recommendations based on the draft prepared by the WHO Secretariat. The GDG considered the relevance of the recommendations for people with SMD based on the GRADE-DECIDE framework (Alonso-Coello *et al.*, 2016):

- the balance of benefit and harm of each intervention;
- values and preferences of people with SMD and their carers;
- costs and resource use;
- acceptability of the intervention to healthcare providers in low- and middle-income countries;
- feasibility of implementation;
- impact on equity and human rights.

The discussion and assessment of values and preferences was based on the knowledge and experience of GDG members. Similarly, no surveys or formal cost-effectiveness studies to determine resource constraints were conducted but discussions of these domains were informed by the combined expertise and experience of the GDG members. Equity and human rights were considered by specifically searching databases that include studies from LMIC, examining data for disaggregation for specific subgroups of people with SMD and when direct evidence for the relevant subgroup was not available, evaluating the indirectness of evidence obtained from other populations. Potential differential effects of the interventions on different subgroups of people with SMD related to economic status, employment or occupation, education, place of residence, gender or ethnicity were considered by the GDG. Equity and human rights considerations were applied to the other criteria in the framework described above by:

- assessing both desirable and undesirable effects for different subgroups of people with SMD;
- examining if some subgroups may value the main outcomes differently than the general population;
- balancing treatment costs with effectiveness;
- varied acceptability of the intervention in different subgroups.

Taking into account these considerations, when making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweighs any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. Strong recommendations imply that most individuals would want the intervention and should receive it while conditional recommendations imply that different choices may be appropriate for individual patients and they may require assistance at arriving at management decisions. In some instances even when the quality of evidence was low or very low, it was agreed that if the recommendation would be of general benefit, and this was seen to outweigh the harms, it

may still be rated as strong. In the event of a disagreement, the chair and the methodologist would ascertain whether the dispute was related to the interpretation of the data or to the way that the recommendation was formulated. If a consensus agreement was not reached, the GDG members agreed to a majority vote of 70% to determine a decision The WHO staff members present at the meeting, as well as other external technical experts involved in the collection and review of the evidence, were excluded from voting. The GDG members reached a consensus agreement on all recommendations and ratings and voting was not needed.

In addition to recommendations, best practice statements were formulated which did not rely on systematic reviews of the evidence but rather on good clinical care and were consensus-based from the GDG.

2.6 DOCUMENT PREPARATION AND PEER REVIEW

In addition to the GDG members, an external review group (ERG) provided expert inputs. The draft guideline and evidence profiles prepared by WHO staff and the GDG were circulated to the external review group and the steering group. The role of the ERG was to identify any errors or missing data and to comment on clarity, setting–specific issues and implications for implementation rather than changing the recommendations. All inputs and remarks were discussed and agreed with the GDG by email.

3. Evidence and recommendations

This section provides an overview of each PICO question described under the following headings: the background; recommendations and additional considerations; supporting evidence for the recommendations and the rationale for the recommendations based on the evidence synthesized as well as criteria listed in the evidence-to-decision tables. The complete evidence profiles for each PICO question including the GRADE tables and the evidence-to-decision tables are available online on the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html). Annex 6 has the drug-drug interaction evidence between medicines relevant for each PICO question and medicines used for SMD.

3.1 TOBACCO CESSATION

For people with SMD who use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) and/or non-pharmacological interventions effective to support tobacco cessation?

Population:
People with SMD who use tobacco

Intervention:
- Pharmacological interventions: including nicotine replacement therapy (NRT), bupropion, varenicline
- Non-pharmacological interventions

Comparison:
Care as usual and/or placebo

Outcomes:
- Critical
  - Tobacco cessation/abstinence rates
  - Tobacco consumption rates
  - Respiratory disease outcomes (COPD, asthma)
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

People with SMD are twice as likely to use tobacco as the general population (around 61% of people with SMD smoke compared to 33% in the general population), to smoke more on average, and are less likely to quit smoking (Centers for Disease Control and Prevention, 2015). People with SMD have been reported to die 15-20 years earlier on average than people in the general population and this is often due to preventable tobacco-related health conditions for example due to heart disease, cancer, and lung disease, which can all be caused by smoking (Trainor and Leavey, 2017). Nicotine has also been shown to have mood-altering effects that can temporarily mask the negative symptoms of mental disorder, putting people with mental disorder at higher risk for cigarette use and nicotine addiction, and tobacco smoke can interact with and inhibit the effectiveness of certain medications taken for mental health conditions and substance abuse (https://www.cdc.gov/tobacco/disparities/mental-illness-substance-use/index.html).

In regard to interventions that have been recommended in the general population for tobacco cessation, bupropion, varenicline and nicotine replacement therapy (NRT) have all been recommended (e.g. mhGAP Intervention Guide, The National Institute for Health and Care Excellence (NICE)), and NICE has also recommended these pharmacological interventions for tobacco cessation for people with mental disorders (NICE guidelines CG178, CG185, CG91. PH48).

RECOMMENDATIONS AND CONSIDERATIONS

In the context of tobacco cessation programmes:

RECOMMENDATION 1:

In people with severe mental disorders, combined pharmacological and non-pharmacological interventions may be considered in accordance with the WHO training package (Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package) (http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/).

(Strength of recommendation: Conditional; quality of evidence: Very low)

RECOMMENDATION 2:

In people with severe mental disorders, a directive and supportive behavioural intervention programme may be considered and should be tailored to the needs of the population.

(Strength of recommendation: Conditional; quality of evidence: Very low)

RECOMMENDATION 3:

In people with severe mental disorders, varenicline, bupropion and nicotine replacement therapy may be considered for tobacco cessation.

(Strength of recommendation: Conditional; quality of evidence: Very low)

BEST PRACTICE STATEMENT:

Prescribers should take into account potential interactions between buproprion and varenicline with psychotropic medications as well as possible contra-indications.

Additional considerations

- Tobacco cessation interventions should be considered as part of broader implementation packages as described in *WHO's MPOWER* (WHO., 2008) package of effective tobacco control measures.
- The behavioral intervention programme can build on the WHO training package and should be tailored to the needs of the population. This is based on the principles of motivational interviewing and aims to increase the person's intrinsic motivation for change based on the person's own personal goals and values.
- Choice of pharmacotherapy will be understandably influenced by resource availability. In people with SMD, varenicline seems to have the highest efficacy, followed by bupropion with or without nicotine replacement therapy, followed by nicotine replacement therapy (nicotine patch) alone.
- Smoking cessation can cause an increase in serum levels of anti-psychotic medication, and smoking cessation needs to be accompanied by a reduction in dose to avoid toxicity. Smoking cessation programmes therefore need to be accompanied by monitoring of clinical state, and where appropriate monitoring of serum levels.

SUPPORTING EVIDENCE AND RATIONALE

Behavioural treatment alone for tobacco smoking cessation has a low abstinence rate in SMD of about 4% which is why combination behavioural treatment and pharmacotherapy is recommended for the population with SMD. At present there is insufficient evidence to indicate whether specialised smoking cessation interventions (vs. standard smoking cessation) and contingent reinforcement i.e. a positive reinforcement technique to increase desired behaviours, in this case tobacco cessation (vs. care as usual) are beneficial for the cessation of smoking in people with SMD. Varenicline's efficacy has been shown to be the highest of the pharmaco-therapy choices for persons with SMD including when compared to bupropion(Anthenelli *et al*., 2016). Evidence for efficacy of bupropion comes from several studies included in the Cochrane review such as the EAGLES trial (Tsoi, 2013); evidence for efficacy of nicotine patch vs. placebo can be seen in the EAGLES trial. While there are no known interactions between NRT or varenicline and medicines used for SMD, there are multiple interactions between bupropion and medicines used for SMD, specifically involving elevated seizure risk and enzymatic inhibition/induction. There is some evidence that people taking buproprion, and varenicline may have increased risk of neuropsychiatric symptoms.

Although the evidence specifically for people with SMD is limited with few studies of small size, WHO has comprehensive tools for tobacco cessation in the general population and the GDG agreed that there was no suggestion of inconsistency with the evidence for tobacco cessation interventions in the general population and in people with SMD. The GDG agreed that the benefits of the interventions outweighed the harms while recognising that prescribers should take into account potential interactions between buproprion with psychotropic medications as well as possible contra-indications of the use of bupropion and varenicline in people with SMD. In view of the low quality evidence, the GDG made conditional recommendations for tobacco cessation interventions in people with SMD.

3.2
WEIGHT MANAGEMENT

3.2.1

For people with SMD who are overweight or obese, are non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies effective to support weight reduction?

Population:
People with SMD who are overweight or obese

Intervention:

- Non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies:
  - Non-pharmacological interventions: e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions
  - Pharmacological interventions: weight-loss medication (e.g. orlistat)
  - Pharmacological management strategies: e.g. switching antipsychotic medication

Comparison:
Care as usual and/or placebo

Outcomes:

- Critical
  - Change in weight
  - Mean BMI (kg/m^2) or change in BMI
- Important
  - Maintenance of weight change/attenuation/prevention of weight gain
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

3.2.2

For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

Population:
People with SMD who are at risk of becoming overweight or obese, e.g. people who have just started anti-psychotic medication

Intervention:
Non-pharmacological interventions, e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions

Comparison:
Care as usual

Outcomes:

- Critical
  - Change in weight
  - Mean BMI (kg/m^2) or change in BMI
  - Maintenance of weight change
  - Attenuation/prevention of weight gain
- Important
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

BACKGROUND

Persons with SMD are 50% more likely to be obese than the general population; different studies have reported obesity rates of around 50% amongst women with SMD, and between around 30 to 40% for men with SMD (Dickerson *et al.*, 2006). People with SMD commonly have poor diets, and tend to consume more sugar and saturated fats than the general population. In addition, they are less likely to exercise, have a high prevalence of low physical activity, and spend over 12 hours on average in sedentary activities everyday (Janney, 2013). Also, increased appetite and metabolic effects of some psychotropic medicines can result in weight gain. Being overweight or obese may be

associated with higher rates of mortality and is related to other cardiovascular risk outcomes. Interventions in the general population have been described in the *Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (2012)* (http://www.who.int/nmh/publications/phc2012/en/).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

Behavioural lifestyle (healthy diet, physical activity) interventions should be considered in all people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese in accordance with *WHO's Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).* These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Strong; Quality of evidence: Very low).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).

Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (2012) (http://www.who.int/nmh/publications/phc2012/en/)

- Advise overweight patients to reduce weight by following a balanced diet.
- Advise patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
- Advise patients to reduce sedentary behaviour and practice regular daily physical activity appropriate for their physical capabilities (e.g. walking).

RECOMMENDATION 2:

For people with severe mental disorders who are overweight or obese, and where lifestyle interventions and/or switching psychotropic medication do not appear successful, adjunctive metformin may be considered. This should be considered under close clinical supervision and monitoring.

(Strength of recommendation: Conditional; Quality of evidence: Low)

BEST PRACTICE STATEMENTS:

- For people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese, initiating a psychotropic medication with lower propensity for weight gain should be considered, taking into account clinical benefits and potential adverse effects.
- For people with severe mental disorders who are overweight or obese, switching to a psychotropic medication with a lower propensity for weight gain may be considered, taking into account clinical benefits and potential adverse effects.

Additional considerations

- Metformin is a commonly used anti-diabetic medication but it can be used for weight loss in people who are not diabetic. Metformin for people with SMD who are overweight or obese:
  - Should preferably be initiated in specialist settings, and should be closely monitored.
  - Should be tried in the short-term before being used in the long-term.
  - Availability may be an issue, i.e. metformin is not reliably available in all settings.
- Fluoxetine may increase the potency of metformin based on the drug-drug interaction searches (Annex 6). Monitor blood glucose control and adjust doses of metformin accordingly, especially when starting or stopping fluoxetine. Risperidone and clozapine are associated with hyperglycaemia and as such may decrease the efficacy of anti-diabetic medication including metformin. Monitor glycaemic control and adjust doses of anti-diabetic medications accordingly.

SUPPORTING EVIDENCE AND RATIONALE

Evidence was extracted from one systematic review with regards to lifestyle interventions for the prevention of weight gain amongst people with SMD who are at risk of becoming overweight/obese, though most of the studies in the review included participants who were already overweight (i.e. BMI over 25) on average. For this reason, the recommendations for the two PICO questions (3.2.1 and 3.2.2) were combined into one when formulating the recommendations.

For non-pharmacological interventions for weight management amongst people with SMD who were already overweight or obese, evidence was extracted from two systematic reviews for short-term lifestyle interventions (Gierisch *et al*., 2013; Naslund et al., 2017), and from one systematic review for long-term lifestyle interventions (Naslund *et al.*, 2017). With regards to anti-psychotic switching from olanzapine, evidence was extracted from one systematic review. Several systematic reviews have reported on the use of metformin for weight management amongst people with SMD who were already overweight or obese; evidence was considered from two systematic reviews when formulating the recommendations (Mizuno *et al*., 2014; de Silva *et al*., 2016).

The systematic reviews revealed very low to low quality evidence from randomized controlled trials for all of these interventions. With regards to all of the included lifestyle interventions, statistically significant effects were reported in favour of all of these. The most consistent evidence was for metformin, as – even though the quality of evidence was very low to low – the six systematic reviews from which evidence was extracted showed positive effects in terms of weight change when compared to placebo. The drug interaction review showed moderate interaction between metformin and some psychotropic medicines (fluoxetine, risperidone and clozapine) for which monitoring of blood glucose and dose adjustment may be needed. Other pharmacological interventions for which statistically significant weight change effects were found in the systematic reviews (Gierisch *et al*., 2013; Mizuno *et al*., 2014) were aripiprazole, reboxetine, sibutramine and topiramate, though the evidence base for these are only emerging and results need to be treated with caution. Sibutramine in particular has been withdrawn from use in several countries due to cardiac risks and so cannot be recommended. There is also some evidence in favour of switching from olanzapine to aripiprazole for the management of weight.

The GDG concluded that the behavioural lifestyle interventions recommended in the WHO guidelines for the general population should be followed in people with SMD since there is some evidence from the general population that advising people to give preference to low glycaemic index foods, follow a balanced diet and advice on exercise may have a beneficial effect on glycaemic control. Although the evidence in the general population is of low quality, these simple interventions are deemed as low-cost, feasible and with a negligible risk of adverse events. The GDG made a strong recommendation for non-pharmacological behavioural/lifestyle interventions, as they concluded that the benefits outweighed the harms including benefits of the intervention on other non-communicable disease outcomes. WHO general population guidelines (WHO PEN) also make a strong recommendation for these interventions in the general population. With regards to pharmacological interventions, the GDG made a strong recommendation for initiating a psychotropic medication with lower propensity for weight gain. The recommendation for switching antipsychotic medication was rated by the GDG as conditional since the quality of the evidence was low and switching antipsychotics because of weight gain should be offset against the risk of relapse of the mental disorder, as well as any potential side effects associated with the newly introduced medication.

3.3
SUBSTANCE USE DISORDERS

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological and/or non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Population:
People with SMD and substance (drug and/or alcohol) use disorder

Intervention:
Pharmacological and/or non-pharmacological interventions for substance use disorders:

- Pharmacological interventions
- Non-pharmacological interventions:
  e.g. motivational interviewing and/or cognitive behaviour therapy (CBT), psychoeducation, brief assessment interview, dual-focus interventions

Comparison:
Care as usual / placebo or one treatment vs another

Outcomes:
- Critical
  - Level of consumption
  - Frequency of use
  - Abstinence
  - Relapse rates
- Important
  - Frequency of adverse events / side-effects

BACKGROUND

Comorbid substance use disorders are the most prevalent psychiatric conditions associated with SMD. The pooled prevalence for comorbid substance use disorders in SMD has been noted to range up to 42% (for alcohol use disorders), 69% (for cannabis use in schizophrenia), and just over 50% (for affective disorder amongst those on a methadone maintenance programme) (McLoughlin *et al*., 2014) (Di Florio, Craddock and van den Bree, 2014). The relationship between substance use disorders and SMD is likely bidirectional and their co-occurrence has been associated with a number of adverse outcomes, including: relapse of the mental disorder and longer hospital admissions, more positive symptoms in people with schizophrenia, and an increased risk of fatal and non-fatal overdoses and suicide.

There have been several Cochrane systematic reviews conducted on interventions for people with substance use disorder (in the general population), which have provided evidence on the effectiveness of the following interventions: Psychosocial interventions, such as combined motivational enhancement therapy (MET) and cognitive behaviour therapy (CBT) with abstinence-based incentives in cannabis use disorder (Gates *et al*., 2016); methadone in people with opioid dependence (Mattick *et al*., 2014). *WHO mhGAP Intervention Guide* provides recommendations for the management of substance use disorders. We have considered these pharmacological and/or non-pharmacological interventions for people with co-morbid SMD and substance use disorder.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and comorbid substance use disorders (drug and/or alcohol) interventions should be considered in accordance with the WHO mhGAP guidelines.

(Strength of recommendation: Conditional; Quality of the evidence: Low).

RECOMMENDATION 2:

Non-pharmacological interventions (e.g. motivational interviewing) may be considered and tailored to the needs of people with severe mental disorders and substance use disorders.

(Strength of recommendation: Conditional; Quality of the evidence: Very low).

WHO mhGAP guidelines

(http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/)

The *mhGAP Intervention Guide* recommends the following:

- **Alcohol use disorders:**
  - Thiamine during alcohol use
  - Diazepam during alcohol detoxification to treat withdrawal symptoms
  - Naltrexone, acamprosate or disulfiram to prevent relapse after detoxification
  - Psychosocial interventions if available, e.g. cognitive behaviour therapy, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups
- **Drug use disorders:**
  - For opioid misuse: buprenorphine, methadone, clonidine, lofexidine, opioid agonist maintenance treatment (OAMT) for relapse prevention.
  - Psychosocial interventions, e.g. CBT, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups.

BEST PRACTICE STATEMENT:

- Prescribers should take into account the potential for drug-drug interactions between medicines used for treatment of substance use disorders and severe mental disorders.

Additional considerations

- Certain side effects (somnolence, hypersalivation, and constipation) may be more prevalent in people treated with clozapine, which should be a consideration when determining choice of pharmacotherapy.

- People with SMD who are injecting drug users may be at an increased risk of Hepatitis B and C through the sharing of contaminated instruments and/ or needles. The Centers for Disease Control and Prevention (CDC) in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with SMD who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA. (https://www.cdc.gov/hepatitis/populations/idu.htm).

SUPPORTING EVIDENCE AND RATIONALE

Evidence of pharmacological interventions for mental disorders comorbid with substance use disorders was extracted from two systematic reviews which focused on antipsychotic prescribing (Wilson and Bhattacharyya, 2016; Temmingh *et al.*, 2018) and one systematic review which focused on antidepressant prescribing in depression comorbid with alcohol use (Agabio *et al.*, 2018). Evidence on psychological interventions for these populations were extracted from two systematic reviews (Hunt *et al.*, 2014; Boniface, 2018).

Detailed reviews revealed very low to low quality evidence from randomized controlled trials, which did not support the superiority of any of the pharmacological interventions against each other. Potential side effects from pharmacological therapies were noted as moderate and will need to be considered when determining the choice of pharmacotherapy. Methadone and buprenorphine, medicines used for treatment of substance use disorders, have major interactions with commonly prescribed psychotropic medications including increased risk of for CNS depression (sedation, confusion, decreased respiratory drive), QT prolongation on ECG, and serotonergic effects (confusion, neuromuscular excitability, and dysautonomia) (Annex 6).

There was no evidence to support superiority of any of the psychosocial interventions against each other in populations with comorbid SMD and substance use disorder. None of the reviewed trials for psychosocial therapies have been conducted in LMIC settings. The absence of high quality evidence does not mean that these treatments do not work but that at present the evidence is of insufficient quality to support the use of one form of non-pharmacological or psychosocial intervention over another in these special populations. One reason for the lack of evidence may be that people with comorbidities are commonly excluded from research (Dennis *et al.*, 2015).

The resource requirements for offering interventions (both pharmacological and psychological) are currently unclear with only one study identified which estimated the cost of providing CBT plus motivational interviewing compared to care-as-usual in a well-resourced setting (USA).

There is good indirect evidence that certain interventions work for alcohol and substance use disorders in the general population, which have been detailed in the current mhGAP 2.0 guidelines, as well as in other guidelines such as those for Opioid Agonist Maintenance Treatment (OAMT) for relapse prevention. The GDG agreed that although the quality of evidence was very low for most psychological interventions in populations with co-morbid SMD and substance use disorders, the psychological interventions which are currently recommended in the MHGAP 2.0 guidelines for the general population (in particular- CBT plus motivational interviewing, motivational interviewing and contingency management) may also be effective in people with SMD . Furthermore, undesirable side effects from non-pharmacological treatments were noted to be trivial. Noting the risk of drug interactions between medicines used for treatment of opioid use disorders and SMD, the GDG agreed that the interactions are outweighed by the risk of other harms of untreated opioid use disorders in people with SMD and rather than withholding opioid replacement therapy, cautious medication management is advised.

Given the low quality of evidence and that all the evidence identified for the treatment of substance use disorders comorbid with SMD came from well-resourced/ high- income settings, the GDG made conditional recommendations.

3.4 CARDIOVASCULAR DISEASE AND CARDIOVASCULAR RISK

3.4.1

For people with SMD and pre-existing cardiovascular disease, what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

Population:
People with SMD and pre-existing cardiovascular disease: e.g. coronary heart disease, prior heart failure or stroke, cardiomyopathy, congenital heart disease, peripheral vascular disease

Intervention:
Pharmacological and/or non-pharmacological interventions

Comparison:
One treatment versus another or care as usual / placebo

Outcomes:

- Critical
  - Major adverse cardiovascular event (MACE) - includes cardiovascular death, myocardial infarction, stroke, heart failure, hospitalization, amputation
- Important
  - Frequency of adverse events/side-effects

3.4.2

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Population:
People with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels)

Intervention:
Pharmacological and/or non-pharmacological interventions:

- pharmacological interventions: a) medication to control high blood pressure; b) medications for high lipid levels
- non-pharmacological interventions

Comparison:
One treatment versus another or care as usual / placebo

Outcomes:

- Critical
  - Adequacy of control of CVD risk factors (a. blood pressure <130/80mmHg; b. cholesterol <200mg/dl)
  - Cardiovascular disease incidence
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

Cardiovascular disease is considered as one of the main potentially avoidable contributors to excess mortality amongst people with SMD. Overall, people with SMD have an approximately 1.5 to 3 times higher risk of cardiovascular morbidity and mortality compared to the general population (Laursen, 2011). There is a complex interplay between several non-communicable diseases, such as diabetes, hypertension and cardiovascular disease, and the presence of SMD. People with SMD are more likely to engage in lifestyle behaviours that contribute to increased cardiovascular risk including tobacco use, harmful use of alcohol, unhealthy diets, and physical inactivity. The iatrogenic effects of medicines used to treat SMDs are linked with increased risk of cardiometabolic diseases. The use of antipsychotic medications has been associated with obesity, insulin resistance, diabetes, myocardial infarctions, atrial fibrillation, stroke, and death.

Pharmacological and non-pharmacological interventions for the general population have been described in the *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings* (WHO, 2010).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and pre-existing cardiovascular disease, or with cardiovascular risk factors (e.g. high blood pressure or high cholesterol), pharmacological and non-pharmacological interventions may be considered in accordance with the *WHO Package of Essential Noncommunicable Disease Interventions* (WHO PEN) for primary care in low-resource settings (2010) for lowering cardiovascular risk and management of cardiovascular disease.

(Strength of recommendation: Strong; Quality of evidence: High to moderate for different interventions).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).

http://www.who.int/cardiovascular_diseases/publications/pen2010/en/

- **Primary prevention of heart attacks and strokes:**
  - Tobacco cessation; regular physical activity 30 minutes a day; reduced intake of salt <5 g per day; fruits and vegetables at least 400g per day
  - Statins and antihypertensives for people with 10-year cardiovascular risk >30%
  - Antihypertensives for people with blood pressure ≥160/100
  - Anthypertensives for people with persistent blood pressure ≥140/90 and 10 year cardiovascular risk >20% unable to lower blood pressure through life style measures
- **Acute myocardial infarction: Aspirin and referral to next level of care**
- **Secondary prevention (post myocardial infarction):**
  - Tobacco cessation, healthy diet and regular physical activity.
  - Aspirin, antihypertensive (low dose thiazide, angiotensin-converting enzyme inhibitor), and statin
- **Secondary prevention (Rheumatic heart disease):**
  - Regular administration of antibiotics to prevent streptococcal pharyngitis and recurrent acute rheumatic fever

RECOMMENDATION 2:

For people with severe mental disorders and pre-existing cardiovascular disease, the following is recommended:

a) **Behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population.**

(Strength of recommendation: Conditional; Quality of evidence: Very low).

b) **Collaborative care, i.e. a multi-professional approach to patient care with a structured management plan, scheduled patient follow-up, and enhanced inter-professional communication, may be considered for cardiovascular management.**

(Strength of recommendation: Conditional; Quality of evidence: Very low).

RECOMMENDATION 3:

For people with severe mental disorders and cardiovascular risk factors, behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Conditional; Quality of evidence: Very low).

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and pre-existing cardiovascular disease:

- Initiating a psychotropic medication with lower propensity for cardiovascular risk is a strategy that should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to a psychotropic medication with lower propensity for cardiovascular risk may be considered, taking into account clinical benefits and potential adverse effects.

For people with severe mental disorders and pre-existing cardiovascular disease or cardiovascular risk factors:

- Prescribers should be aware of potential interactions between prescribed medicines for cardiovascular disease and prescribed psychotropic medications, which may affect cardiovascular risk. Cardiovascular outcomes and risk factors should be monitored and dose adjustment of cardiovascular medicines may be required.

SUPPORTING EVIDENCE AND RATIONALE

For people with SMD and pre-existing cardiovascular disease, two systematic reviews were included that reported on anti-depressants as compared to care as usual (Maslej *et al.*, 2017; Nieuwsma *et al.*, 2017); one systematic review was included that reported on psychosocial interventions (Ski *et al.*, 2016); and one systematic review each for exercise therapy (Verschueren *et al.*, 2018) and collaborative care (Tully and Baumeister, 2015).

For people with SMD and cardiovascular risk (e.g. high blood pressure or cholesterol), regarding the use of pharmacological interventions, two systematic reviews were used to extract evidence on the use of metformin versus placebo (Mizuno *et al.*, 2014; de Silva *et al.*, 2016), and two on the use of aripiprazole versus placebo (Gierisch *et al*, 2013; Mizuno *et al*, 2014), in the management of either blood pressure or cholesterol, or the frequency of adverse effects. Two systematic reviews were included that reported on non-pharmacological interventions as compared to care as usual (Gierisch *et al*, 2013; Teasdale *et al*, 2017). None of these systematic reviews included cardiovascular disease incidence as an outcome which is one of the critical outcomes for this PICO question. All of the systematic reviews and meta-analyses for comorbid cardiovascular disease focused on interventions for people with depression. No reviews assessed interventions in populations with other SMD (e.g. schizophrenia, bipolar disorder) with comorbid cardiovascular disease. The evidence and recommendations are therefore indirect for populations with SMD and comorbid cardiovascular disease.

No sufficiently high-quality systematic reviews could be identified that reported on either pharmacological or non-pharmacological interventions compared to another treatment, either for SMD and pre-existing cardiovascular disease or cardiovascular risk.

The systematic reviews revealed either very low or low quality evidence from randomized controlled trials for all of these interventions; the only exception to this was for psychosocial interventions for people with SMD and pre-existing cardiovascular disease, for which some of the evidence was graded as moderate quality. The only included intervention for which statistically significant effects were reported for people with SMD and pre-existing cardiovascular disease was collaborative care, which may show a relative and absolute reduction in major adverse cardiac events in the short to medium-term (less than 12 months), though it is less clear whether this is the case in the longer-term (over 12 months).

Major drug-drug interactions were found between several psychotropic medications and commonly prescribed medications for cardiac conditions, hypertension and cholesterol control. Some examples of these are: the risk of hypotension or beta-blocker toxicity (including hypotension, bradycardia, and heart block/prolonged PR interval) with beta blockers and the risk of hypotension with diuretics (Annex 6).

Given the evidence was limited for people with SMD, the GDG used evidence from general populations and thought it to be applicable because they would benefit people with SMD too. However, the GDG agreed that it is important to exercise caution in the initiation of psychotropic medication due to the heightened risk of cardiovascular disease and potential drug interactions. There is currently insufficient evidence for behvioural lifestyle interventions for people with SMD and cardiovascular disease and risk, conditional recommendations have been made for these interventions as the GDG agreed that there the benefits outweighed the risks including benefits of the intervention on other non-communicable disease outcomes.

3.5 DIABETES MELLITUS

For people with SMD and diabetes mellitus, what pharmacological and/or non-pharmacological interventions are effective to improve glycaemic control?

Population:
People with SMD and diabetes mellitus

Intervention:
- Pharmacological interventions: e.g. medication to treat diabetes
- Non-pharmacological interventions: e.g. behavioural lifestyle interventions, cognitive behaviour therapy

Comparison:
One treatment versus another or care as usual

Outcomes:
- Critical
  - Fasting blood glucose <120mg/dl; post-prandial blood glucose<160mg/dl
  - Glycosylated haemoglobin A1c (HbA1c<7 for people below 60 years and 7-8 for people above 60 years with other risk factors)
  - Diabetes complications – Major Atherosclerotic Cardiovascular Events (MACE), chronic kidney disease, diabetic retinopathy, diabetic neuropathy, hospitalization for infection
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

There is high co-morbidity between SMD and diabetes mellitus. People with SMD are at an increased risk of diabetes (around double for schizophrenia and bipolar disorder, and 1.5 times the risk for depression), and people with diabetes are at a heightened risk of SMD (around double for depression), with a higher risk in low- and middle-income countries(Vancampfort et al., 2016). However, this often goes undetected, and people with comorbid SMD and diabetes have an increased risk of mortality. There is an association with diabetes with some anti-psychotics, anti-depressants and lithium, as well as with health-related behaviours (such as physical activity and diet), other environmental factors, and gender (elevated risk in women).

This section covers evidence regarding pharmacological and/or non-pharmacological interventions for people with SMD and diabetes mellitus. The inclusion of interventions was guided by the research evidence available for people with diabetes and SMD.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and diabetes mellitus, interventions in accordance with the *WHO Package of Essential Non-communicable (PEN) Disease Interventions for primary care in low-resource settings* should be considered for diabetes management

(Strength of recommendation: Strong; Quality of evidence: Low).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010)

http://apps.who.int/iris/bitstream/handle/10665/133525/9789241506557_eng.pdf;jsessionid=C8B92D24C7F27E9E3BEBC2957FB8CCE8?sequence=1

- **For Type 1 diabetes:**
  - Daily insulin injections
- **For Type 2 diabetes:**
  - Anti-diabetic agents for type 2 diabetes, if glycaemic targets are not achieved with modification of diet, maintenance of a healthy body weight and regular physical activity
  - Metformin as initial drug in overweight patients and non-overweight
  - Other classes of anti-diabetic agents, added to metformin if glycaemic targets are not met
  - Reduction of cardiovascular risk for those with diabetes and 10-year cardiovascular risk >20% with aspirin, angiotensin converting enzyme inhibitor and statins

WHO NCD 2012: Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings

(http://www.who.int/nmh/publications/phc2012/en/):

- **Diagnosing diabetes:** Laboratory services. If not available, point of care devices may be used
- **Glycaemic control:** Diet and physical activity as first-line treatment, Metformin as first-line oral hypoglycaemic agent where diet is not sufficient, sulfonylureas for those patients where metformin is not effective/patient has contraindications
- **Reducing the risk of cardiovascular disease and diabetic nephropathy:** Statins for all people with Type-2 diabetes over 40 years of age, antihypertensive agents to reduce blood pressure, choice of antihypertensive agent
- **Prevention of lower limb amputations:** Educate patients and health care workers
- **Prevention of blindness:** Screening for diabetic retinopathy
- **Severe hypoglycaemia, hypoglycaemic emergencies**: Intravenous hypertonic glucose treatment or glucose (dextrose) for unconscious patients, referral to hospital and drip in emergencies

RECOMMENDATION 2:

Behavioural lifestyle interventions should be considered for all people with severe mental disorders and diabetes mellitus. These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Strong; Quality of evidence: Very low).

RECOMMENDATION 3:

In people with depression and comorbid diabetes mellitus, cognitive behaviour therapy for treatment of depression may be considered.

(Strength of recommendation: Conditional; Quality of evidence: Very low).

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and diabetes mellitus:

- Initiating an anti-psychotic medication with lower propensity for producing hyperglycaemia should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to an anti-psychotic medication with lower propensity for producing hyperglycaemia is a strategy that may be considered, taking into account clinical benefits and potential adverse effects.
- Prescribers should be aware of potential interactions between prescribed medicines for diabetes and prescribed psychotropic medicines, which may affect glycaemic control. Glycaemic control should be monitored and dose adjustment of medicines may be required.

SUPPORTING EVIDENCE AND RATIONALE

With regards to pharmacological interventions for people with SMD and diabetes, one (the same) systematic review was used to extract evidence for diabetes medication, weight loss medications, anti-psychotic switching, and weight loss and diabetes medications combined.

The systematic reviews revealed very low quality evidence from randomized controlled trials for all of these interventions. There was some evidence to suggest anti-psychotic switching had beneficial effects. The drug-drug interaction review showed moderate interactions between some psychotropic medicines and anti-diabetic medicines (increased or decreased potency of the anti-diabetic medicine) that requires blood glucose monitoring and dose adjustment of anti-diabetic medicines.

With regards to non-pharmacological interventions, evidence from one systematic review each was considered for behavioural interventions (Taylor *et al.*, 2017) and cognitive behaviour therapy (Li *et al.*, 2017), and one systematic review for self-management interventions (McBain *et al.*, 2016). There was some evidence that cognitive behaviour therapy for treatment of depression shows positive effects on blood glucose amongst people with diabetes and comorbid depression (probably by eliminating the negative effects of depression on diabetes). There is insufficient evidence available for the management of diabetes amongst people with SMD for all other reviewed interventions.

Since all of the evidence was rated as very low in quality, and there was insufficient evidence available for most of the reviewed interventions, the GDG concluded that the WHO guidelines for the general population in low-resource settings should be followed as a first step as the underlying pathophysiological mechanisms would be similar in people with SMD. Nevertheless, the GDG made additional best practice statements for the initiation of psychotropic medication and potential drug-drug interactions, to counter the risks of taking these medications. A strong recommendation has also been made for behavioural lifestyle interventions despite very low quality evidence as the GDG agreed that the benefits outweighed the harms and as there is a strong recommendation for this by WHO for the general population (WHO PEN). The GDG also concluded that there are benefits of the intervention on other noncommunicable disease outcomes. The GDG made a conditional recommendation for cognitive behaviour therapy because of very low quality evidence and the possible lack of generalizability to all people with SMD.

3.6 HIV/AIDS

For people with SMD and HIV/AIDS, what pharmacological (i.e. antiretroviral drugs, psychopharmacology) and nonpharmacological interventions are effective to support reduction in HIV-related outcomes?

Population:
People with SMD and HIV/AIDS

Intervention:
- Pharmacological interventions (e.g. antiretroviral drugs, psychopharmacology)
- Nonpharmacological interventions

Comparison:
One treatment versus another or care as usual

Outcomes:
- Critical
  – HIV-related outcomes
- Important
  – Frequency of adverse events/side-effects

BACKGROUND

The association between mental health disorders and HIV/AIDS is complex and bi-directional - they frequently co-occur: mental disorders can be precursors to HIV/AIDS, consequences of HIV infection, or the result of interactive effects. They also have similar consequences in terms of their public health, social, and economic impacts.

International evidence has found that populations with SMD have higher rates of HIV infection. Among persons with SMD, the median prevalence of HIV in the US is 1.8 % (range: 0.1%-5.0%) with a high rate among inpatient populations (3.8%), whereas the overall US adult population estimated prevalence of HIV is 0.5% (Janssen *et al.*, 2015). HIV rates may be even higher in certain vulnerable populations, such as those who have SMD and are also homeless(Susser, Valencia and Conover, 1993). People with SMD and HIV experience a complex set of medical, psychological and social complications that need to be tackled through integrated care. The interventions included pharmacological interventions for SMD and HIV as well as non-pharmacological interventions such as psychosocial support.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and HIV/ AIDS, antiretroviral drugs should be considered in accordance with the WHO Updated recommendations on first-line and second-line antiretroviral regimens.

(Strength of the recommendation: Strong; Quality of the evidence: Moderate)

Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (WHO/ CDS/HIV/18.45). Licence: CC BY-NC-SA 3.0 IGO.

http://www.who.int/hiv/pub/guidelines/ARV2018update/en/

RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS

A DTG based regimen is recommended as a preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)

- Adults and adolescents (moderate-certainty evidence)
- Women and adolescent girls of childbearing potential (very-low-certainty evidence)
  Note of caution on using DTG during the periconception period and for women and adolescent girls of childbearing potential*
- Exposure to DTG at the time of conception may be associated with neural tube defects among infants.
- DTG appears to be safe when started later in pregnancy: after the period of risk of neural tube defects, up to eight weeks after conception.
- Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; based on limited data, hormonal contraception and DTG have no reported or expected drug–drug interactions.
- An EFV-based regimen is a safe and effective first-line regimen recommended for use by the WHO 2016 ARV drug guidelines and can be used among women of childbearing potential during the period of potential risk for developing neural tube defects (at conception and up to eight weeks after conception).

Further guidance on the treatment and care of people living with HIV can be found in *"Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd edition 2016."* http://www.who.int/hiv/pub/arv/arv-2016/en

[List of abbreviations: DTG: dolutegravir; EFV efavirenz]

* an ongoing observational study in Botswana recently identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. WHO is taking this potential safety issue seriously and is working closely with all relevant stakeholders to further investigate these preliminary findings. WHO will update these guidelines and provide additional information as it becomes available

RECOMMENDATION 2:

Additional psychosocial support for treatment adherence should be provided to people with HIV and severe mental disorders in accordance with the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.

(Strength of the recommendation: Strong; Quality of the evidence: Moderate)

Adherence support interventions extracted from WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. 2016

http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

RECOMMENDATION: Adherence support interventions should be provided to people on ART (strong recommendation, moderate-quality evidence).

The following interventions have demonstrated benefit in improving adherence and viral suppression:

- peer counsellors (moderate-quality evidence)
- mobile phone text messages (moderate-quality evidence)
- reminder devices (moderate-quality evidence)
- cognitive-behavioural therapy (moderate-quality evidence)
- behavioural skills training and medication adherence training (moderate-quality evidence)
- fixed-dose combinations and once-daily regimens (moderate-quality evidence).

Considerations in specific populations: People with HIV with uncontrolled depressive symptoms are more likely to have poor adherence to ART. Adherence is complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Counselling for HIV and depression and appropriate medical therapies for people with mental disorders can help to improve adherence. WHO recommends that assessment and management of depression should be included in care services for all people living with HIV.

BEST PRACTICE STATEMENT:

For people with severe mental disorders and HIV/ AIDS prescribers should take into account the potential for drug-drug interactions between antiretroviral drugs and psychotropic medicines.

SUPPORTING EVIDENCE AND RATIONALE

There is limited RCT evidence for pharmacological treatment in people with SMD and HIV/AIDS. One systematic review that was included in the evidence profile assessed the efficacy of antidepressant therapy for treatment of depression in people with HIV/AIDS (Eshun-Wilson, 2018). The evidence was of very low quality and the results inconclusive. The drug interaction review reveals multiple interactions between efavirenz and psychotropic medicines, specifically involving the risk of QT interval prolongation, CNS depression and /or enzyme induction (Annex 6). No reviews were identified for non-pharmacological treatments including adherence management specifically in people with SMD and comorbid HIV/ AIDS.

These recommendations are based on indirect evidence of HIV treatment in the general population that are provided in existing WHO guidelines that strongly recommend ARV and adherence management to support ARV adherence in people with HIV/AIDS with or without SMD. The GDG concluded that the balance between desirable and undesirable effects favor the intervention leading to strong recommendations while noting the need to consider drug interactions. They also concluded that there was no important uncertainty about or variability in how much people value the main outcomes and that the interventions would increase health equity. The GDG agreed that people with SMD would need additional support for adherence as the presence of SMD and its associated symptoms can have a detrimental impact on adherence to ARV and progression of AIDS.

3.7
OTHER INFECTIOUS DISEASES (TUBERCULOSIS, HEPATITIS B/C)

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and nonpharmacological (social, psychological) interventions are effective for treatment of infectious diseases (i.e. tuberculosis, hepatitis B, hepatitis C)?

Population:
People with SMD and infectious diseases (Tuberculosis, Hepatitis B/C)

Intervention:

- Pharmacological interventions for infectious diseases
- Nonpharmacological (social, psychological) interventions for infectious diseases

Comparison:
One treatment versus another or care as usual

Outcomes:

- Critical
  – Infectious disease-related outcomes
- Important
  – Frequency of adverse events/side-effects

BACKGROUND

People with SMD are at greater risk than the general population for exposure to infectious diseases, including tuberculosis (TB) and chronic hepatitis(Rosenberg *et al.*, 2010). Infectious diseases appear to contribute to an increased risk of death in persons with SMD, with a 4- to 8-fold risk of death due to infection compared to the general population.

Tuberculosis and SMD share common risk factors including homelessness, HIV positive serology, alcohol/substance abuse and migrant status leading to frequent co-morbidity. There are widespread discriminatory attitudes and behaviours towards patients with TB and SMD in the community which affects health-related quality of life. In people with SMD and TB, there may be a negative impact on health behaviours such as medication adherence leading to greater morbidity, mortality, amplification of drug-resistance, transmission and all the associated social costs of these outcomes (Alene *et al.*, 2018).

The WHO End TB strategy calls to provide TB care through an integrated approach in collaboration with other public health programmes including mental health services such as tailoring TB care delivery models to the specific needs of populations with mental health problems.

There is also a high prevalence of hepatitis B and C in people with SMD. There is evidence that hepatitis C infection itself may be directly associated with psychiatric symptoms, independent of pre-existing psychiatric disorders. Stigmatization and the fact that people have to cope with a chronic infectious disorder increase the risk of depression. As is seen with TB, mental health problems during antiviral treatment have a strong impact on quality of life, may reduce treatment compliance and are risk factors for treatment failure.

For people with SMD and TB or hepatitis B/C, pharmacological and non-pharmacological interventions need to be considered as in the general population.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and TB, pharmacological management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care*, and the *WHO treatment guidelines for drug-resistant tuberculosis*.

(Strength of the recommendation: strong; Quality of the evidence: Low).

WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care

(http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)

In patients with drug-susceptible pulmonary TB, the 6-month rifampicin-based regimen 2HRZE/4HR and daily dosing is the recommended regimen and dosing frequency.

WHO treatment guidelines for drug-resistant tuberculosis

(http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1).

Note: The guidelines are currently being updated and the recommendations will be replaced with the revised ones as soon as they are available.

1) Shorter MDR-TB regimen

In patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens (conditional recommendation, very low certainty in the evidence).

2) Longer MDR-TB regimens

2a) In patients with RR-TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C2 (conditional recommendation, very low certainty in the evidence). If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five.

2b) In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).

(Group A=levofloxacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C= ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine).(Group D2=bedaquiline, delamanid; Group D3=p-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin clavulanate, (thioacetazone)).

RECOMMENDATION 2:

For people with severe mental disorders and TB, non-pharmacological (social, psychological) management should be considered in accordance with the WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care, and the WHO treatment guidelines for drug-resistant tuberculosis.

(Strength of the recommendation: strong; Quality of the evidence: Low).

Cross-cutting interventions for drug-susceptible TB and drug-resistant TB: effectiveness of patient care and support interventions

(http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)

RECOMMENDATIONS:

Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. (Strong recommendation, moderate certainty in the evidence)

A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option. (Conditional recommendation, low certainty in the evidence)

One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a) tracers and/or digital medication monitor (Conditional recommendation, very low certainty in the evidence) b) material support to patient (Conditional recommendation, moderate certainty in the evidence) c) psychological support to patient (Conditional recommendation, low certainty in the evidence) d) staff education (Conditional recommendation, low certainty in the evidence).

[The GDG suggests that psychological support* should be provided to patients with TB (conditional recommendation, low certainty of evidence). *Psychological support includes counselling sessions and peer-group support.]

Psychological support was varied and could include self-help groups, alcohol cessation counselling and TB clubs. Patients who had access to psychological support had higher rates of treatment completion and cure, as well as lower rates of treatment failure and loss to follow-up. When considering this data, it should also be noted that psychological support types are very broad and may not be adequately represented in this review. To maximize health equity, psychological support should be targeted at the most marginalized populations.

RECOMMENDATION 3:

For people with severe mental disorders and hepatitis B, treatment should be considered in accordance with the WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.

(Strength of the recommendation: strong; Quality of the evidence: Low)

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015

http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1

In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. *(Strong recommendation, moderate quality of evidence)*

RECOMMENDATION 4:

For people with severe mental disorders and hepatitis C, treatment should be considered in accordance with the WHO guidelines for the screening care and treatment of persons with chronic hepatitis C infection.

(Strength of the recommendation: strong; Quality of the evidence: Low)

Guidelines for the screening care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016

http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

Treatment with direct-acting antiviral agents: it is recommended that direct-acting antivirals (DAA) regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon and ribavirin. *(Strong recommendation, moderate quality of evidence)*

BEST PRACTICE STATEMENT:

For people with severe mental disorders and TB, Hepatitis B/C prescribers should take into account the potential for drug-drug interactions between TB medicines, medicines for hepatitis B and C with psychotropic medicines.

Additional considerations

People with SMD may be at an increased risk of Hepatitis B and C for example due to injection drug use. The CDC in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with SMD who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA (https://www.cdc.gov/hepatitis/populations/idu.htm).

SUPPORTING EVIDENCE AND RATIONALE

No reviews were identified for interventions in people with SMD and comorbid TB, Hepatitis B/C. A recent systematic review reported that programmes that included educational, psychological, and/or material support were associated with better TB outcomes, and can now be considered best practice(Alipanah *et al*., 2018). Some trial evidence shows effectiveness of treatment of pulmonary TB in people with SMD (Mishin *et al* 2008) and of a brief intervention to deliver best practice services for infectious diseases to people with mental disorders in increasing participation and acceptance of core services, including testing for hepatitis B/C; immunization for hepatitis A and B; increased hepatitis knowledge reduction of substance use (Rosenberg *et al*., 2010).

The drug-drug interaction review showed that major interactions exist between medicines used for TB, hepatitis B/C and psychotropic medicines (Annex 6). These require close clinical monitoring and dose adjustments and in some cases use of alternate psychotropic medicines with less potential for interaction.

These recommendations are based on indirect evidence of TB/Hepatitis treatment in the general population that are provided in existing WHO guidelines as the GDG concluded that the same pathophysiological mechanisms for these conditions would apply to people with SMD. The GDG provided strong recommendations as they agreed that the benefits of the interventions outweighed the harms while noting the need to consider drug interactions. The GDG also agreed that there was no important uncertainty about or variability in how much people value the main outcomes and that the interventions would increase health equity. The GDG agreed that people with SMD would need additional support for adherence to TB treatments and provided a strong recommendation for this intervention drawing from existing general population guidelines.

4. Implementation considerations

The recommendations in these guidelines must be implemented using a person-centred and integrated approach to address factors associated with excess mortality in persons with SMD. This integration is needed at four levels – screening and early detection of physical health conditions, counselling for behavioural risk factors, assessment and management of cardiovascular disease risk and management of established physical and mental health conditions.

We propose a multilevel intervention framework that will be useful for designing, implementing and evaluating interventions and programmes to reduce excess mortality in persons with SMD (Liu et al., 2017). The first level is individual-focused interventions. The second and third levels of the framework consist of strategies focussed on the health systems and socio-environmental context, respectively, which provide the enabling environment for implementation of the recommendations.

The ***individual-focused interventions*** i.e. strategies delivered to individuals with SMD to target their mental health condition, physical health and lifestyle behaviours should be guided by the recommendations proposed in these guidelines.

Health screening facilitates early detection and treatment for many of these conditions, though rates of screening in people with SMD appear to be reduced compared with the general population. A UK survey(Patel *et al.*, 2014) found that only 33% of people with schizophrenia had received adequate cardiovascular disease screening in the previous 12 months. Effective interventions for increasing access to, or uptake of, screening for a range of conditions in the general population (Camilloni *et al.,* 2013) exist. A recent review identified interventions to increase both access to and uptake of physical health screening in people with SMD amongst which are staff and stakeholder involvement in screening, staff flexibility when taking physical measurements (e.g. using adapted equipment) and strong links with primary care (Lamontagne-Godwin *et al.*, 2018).

Psychosocial interventions that promote adherence in people with SMD are particularly important when addressing physical health conditions. This can also take the form of generic advice and psychoeducation at the time of diagnosis of the SMD.

Adherence to medication guidelines − such as the American Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations (Kreyenbuhl *et al.*, 2010) − appear to have an effect on reducing mortality in schizophrenia. These, along with other specific recommendations for psychosocial treatments as described in these guidelines, are important considerations when developing intervention plans for people with SMD. The full participation of persons with SMD in their treatment and recovery plans is a very important factor in improving health outcomes (Vahdat *et al.*, 2014).

The next level in the framework encompasses strategies within ***health systems*** targeting health care providers and service delivery components. These will vary across different settings depending upon many parameters, such as the number of specialists versus primary care providers, the different distribution of health risk factors, the presence or absence of universal health care, and the availability of health technologies and medications. Strengthening of the six building blocks of the health systems – service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance (stewardship) – would improve outcomes for persons with SMD.

Care coordination, collaborative care or integrated care programmes that include support to better equip health systems, usually through the provision of additional supportive members who can serve as a liaison between mental health and physical health care systems or through linking of delivery of physical and mental health services are particularly important. Mental health practitioners need to be better at physical health skills, as well as physical health clinicians/ systems being better at addressing needs of people with SMD.

In countries with limited resources, evidence suggests that mental health care can be delivered effectively in primary health-care settings, through community-based programmes and task-shifting approaches. Non-specialist health professionals, lay workers, affected individuals, and caregivers with brief training and appropriate supervision by mental health specialists are able to detect, diagnose, treat, and monitor individuals with mental disorders and reduce caregiver burden. Physical health in people with SMD should also be considered in community-based programmes and task-shifting approaches (Kakuma *et al.*, 2011).

The broadest level of the framework incorporates ***socio-environmental factors*** and the social determinants of health. This part of the model acknowledges the range of potential strategies originating from the community to address contributors to premature mortality such as peer and family support programmes and stigma reduction programmes. At a wider level, public health policies providing mental health parity are essential to improve lives of those with SMD. A twin-track approach is likely to work best with improved public health for all, recognising that the broader social determinants like poverty affect certain groups more, and, targeted interventions for at-risk groups. Strategies at the policy level that affect screening or management of HIV, TB or tobacco consumption are especially relevant to those with SMD and may have even greater effects on the health and well-being of this high-risk population.

The recommendations contained in these guidelines should be adapted into a locally appropriate document that can meet the needs of each country and its health services. WHO headquarters will work closely with the regional and country offices, as well as implementing partners, to ensure communication and country-specific adaptations of the guidelines, through regional and national meetings.

As countries consider how to implement these guidelines, the budgetary and human resource requirements, and other health systems implications should be analysed to identify which inputs and systems are currently available, and which areas require additional investment, including training of health workers; supply of medicines; and adaptations of health information systems to collect data on service utilization.

To support country implementation, WHO will produce a series of subsidiary tools that will address clinical and service delivery aspects of the implementation of the recommendations included in these guidelines.

5. Publication, dissemination, and evaluation

5.1 PUBLICATION AND DISSEMINATION

The guidelines are disseminated as a print publication and electronically on a dedicated internet space on the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html).

WHO publications, training and clinical management manuals will be revised to reflect the updated recommendations. A range of subsidiary products will be developed to support the implementation including job aids and policy briefs.

The guidelines and products are developed in English, and will be translated into other WHO official languages for wider dissemination and in collaboration with WHO Regional Offices.

Dissemination will be supported by publication of selected systematic reviews and evidence in peer review journals, and presentations and workshops at key conferences and events.

5.2 MONITORING AND EVALUATION

Implementation of the recommendations will be monitored at the health facility level. Facility data will be collected through surveys or routine health information systems. Special studies can be considered where routine monitoring is not feasible or appropriate.

WHO will continue to solicit and collect regular feedback through process indicators by Ministries of Health regarding implementation activities in order to evaluate the impact and usefulness of this guideline. This feedback will also identify areas where improvement is warranted.

5.3 IMPLICATIONS FOR FURTHER RESEARCH

While evidence for mental health treatments is strong, the evidence for effectiveness of interventions to prevent and treat physical conditions in those with SMD is limited. Interventions developed for the general population geared at non-communicable diseases, infectious diseases or other health problems are likely as effective for persons with SMD but given the special needs of this population, interventions for SMD require tailoring. However, more research is needed on the degree of tailoring required. For this, it is essential to include people with SMD in research studies to a much greater extent than is being currently done.

For current evidence-based interventions, research is needed on optimal length and dose needed to positively affect health, which will also be important for resource allocation. Multimodal approaches, which can include behavioural plus pharmacological interventions and include components such as peer support or technology are promising, but have yet to be studied systematically to clarify whether or which multicomponent programs are effective, and which components of the intervention are most beneficial. Many people with SMD have multiple cardiovascular and other risk behaviours which may be modifiable, and future research should test interventions addressing multiple risk factors, as well as those which are directly linked to mortality.

Cost-effectiveness models of different approaches in people with SMD are important, especially in low resource settings, as we aim to achieve universal health coverage and to address the physical health needs of this vulnerable population.

Research is needed to identify and manage barriers to and facilitators of implementing evidence-based guidance and policy recommendations. We need to understand how to deliver evidence-based interventions successfully in the real world, taking into account training and workforce issues and often-limited resources in local community settings. We need to understand to what extent interventions and programmes could or should be disseminated across countries.

Another important area of research will be to assess the effects of health system and policy interventions on excess mortality in SMD. We need to understand why those with SMD have not benefitted from trends in the general population towards reduced mortality in some diseases and smoking cessation. Researchers should take advantage of natural experiments and also design studies in health systems and at the population level to evaluate the impact of these programmes.

Finally, to gain a better understanding of the different perspectives involved, qualitative research is needed to understand the experiences of users, providers, family members, as well as professionals' receptivity to education and training.

5.4 FUTURE REVIEW AND UPDATE

These guidelines will be reviewed in three to five years, unless an earlier review and update is warranted by breakthrough research. New evidence in these areas is regularly monitored by the WHO Secretariat, in consultation with GDG members and technical experts identified for the evidence review process, WHO collaborating centres, and academic institutions.

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Annex 1. Guideline Development Group (GDG) members

	Name	Gender	WHO Region	Affiliation	Area of expertise
1.	**Abdullah Al Khathami**	M	**EMR**	Ministry of Health, Saudi Arabia	Family and community medicine, medical education, program management
2.	**Corrado Barbui**	M	**EUR**	University of Verona, Italy	Mental health research and training, public health, health systems strengthening
3.	**Jackie Curtis**	F	**WPR**	University of New South Wales, Australia	Psychiatry, early psychosis, comorbidity
4.	**Gail L. Daumit**	F	**AMR**	Johns Hopkins Medical Institutions, Division of General Internal Medicine, Welch Center for Prevention, Epidemiology and Clinical Research Baltimore, USA	Psychiatry, Epidemiology, Health Policy and Management and Mental Health
5.	**Chris Dowrick**	M	**EUR**	University of Liverpool, Institute of Psychology, Health and Society	Medically unexplained somatic complaints, mental health in primary care, guideline development (NICE) for depression
6.	**Benjamin Druss**	M	**AMR**	Center for Behavioural Health Policy Studies, Rollins School of Public Health, 1518 Clifton Rd, Atlanta, USA	Health policy, health outcomes and mental health
7.	**Rabih El Chammay**	M	**EMR**	Ministry of Health, Beirut, Lebanon	Public mental health, mental health policy, health equity
8.	**Suhaila Ghuloum**	F	**EMR**	Weill Cornell Medicine, Qatar Hamad Medical Corporation, Qatar	Mental health service planning, schizophrenia, psychiatric epidemiology
9.	**Oye Gureje**	M	**AFR**	Department of Psychiatry, University College Hospital, Ibadan, Nigeria	Global mental health; epidemiology; aging; health system strengthening; classification of mental disorders
10.	**Yueqin Huang**	F	**WPR**	National Clinical Research Center for Mental Disorders, Peking University Sixth Hospital, Peking University Institute of Mental Health, China	Psychiatry, child behavioural and developmental disorders, self-harm, suicide, depression
11.	**Asma Humayun**	F	**EMR**	Meditrina Health Care, Pakistan	Depression, psychosocial support and interventions for mental disorders

	Name	Gender	WHO Region	Affiliation	Area of expertise
12.	**Thomas Munk Laursen**	M	**EUR**	National Centre for Register-Based Research, Aarhus University, School of Business and Social Sciences, Institute of Economics and Business, Aarhus, Denmark	Research in schizophrenia and bipolar disorder
13.	**Mario Maj**	M	**EUR**	Department of Psychiatry, University of Naples, Italy	Research in bipolar disorder, psychiatric comorbidity, classification of mental disorders
14.	**Soontareeporn Meepring**	F	**WPR**	Department of Nursing, Faculty of Nursing, Naresuan University, Phitsanulok, Thailand	Physical health in people with SMD, technology in mental health
15.	**Shanthi Mendis**	F	**SEAR**	Independent consultant in Global Health, Sri Lanka	Noncommunicable diseases and cardiology, health policy development, capacity strengthening, implementation research particularly in low- and middle-income countries.
16.	**Dorairaj Prabhakaran**	M	**SEAR**	Centre for Chronic Conditions and Injuries and Vice President, Public Health Foundation of India, Haryana, India	Cardiovascular disease prevention, epidemiology, developmental origin, and biomarkers of cardiovascular diseases and diabetes
17.	**Martin Prince**	M	**EUR**	King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, UK	Dementia, global mental health, guidelines development, dementia in LMIC
18.	**Thara Rangaswamy**	F	**SEAR**	Schizophrenia Research Foundation, Chennai, India	Mental health research, policy and advocacy
19.	**David Shiers**	M	**EUR**	Psychosis Research Unit, Greater Manchester Mental Health Trust, UK; Division of Psychology and Mental Health, University of Manchester, UK	Early intervention, physical health in people with SMD, health inequality
20.	**Ezra Susser**	M	**AMR**	Columbia University, 722 West 168th Street, New York, USA	Psychiatric epidemiology, research on course and outcome of schizophrenia, homelessness
21.	**Graham Thornicroft**	M	**EUR**	Health Service and Population Research Department, King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, UK	Global mental health, guidelines development, mental health services research, mental health stigma, health equity.
22.	**Abe Fekadu Wassie**	M	**AFR**	Department of Psychiatry, College of Health Sciences, Addis Ababa University, Ethiopia	Psychopharmacological studies, service development, cultural aspects of depression, programme management

Annex 2. Assessment of conflict of interest

INDIVIDUALS INVOLVED IN ASSESSMENT OF CONFLICT OF INTEREST:

Shekhar Saxena, Director
Department of mental health and substance abuse
WHO headquarters

Tarun Dua, Programme manager
Department of mental health and substance abuse
WHO headquarters

Neerja Chowdhary, Technical officer
Department of mental health and substance abuse
WHO headquarters

To comply with WHO's Conflict of Interest Policy, the Secretariat followed the revised Guidelines for Declaration of Interests (WHO Experts)[1]. Declarations of interest (DoI) were requested from a) all GDG members b) all external partners involved in the evidence review process; c) all experts invited to review the evidence profiles.

A letter requesting completion of a DoI form and submission of a curriculum vitae was sent to all GDG members, the external review group and external partners. They were asked to agree to the publication of a summary of declarations in the guideline. The GDG members were also required to complete a confidentiality undertaking. Once received, the WHO Secretariat reviewed the DoIs as well as additional information (internet and bibliographic database search) and evaluated if there are any conflicts of interest and if so, whether these require a management plan.

In order to enhance its management of conflicts of interest as well as strengthen public trust and transparency in connection with WHO meetings and activities involving the provision of technical/normative advice, the names and brief biographies of members being considered for participation in the GDG were disclosed for public notice and comment prior to the meeting.

At the beginning of the GDG meeting, the DoI of each GDG member were presented and GDG members and external partners were asked to update their DoI with relevant changes by notifying the responsible technical officer.

[1] WHO Office of Compliance, Risk Management and Ethics (CRE) http://intranet.who.int/homes/cre/ethics/doiexperts/

The follow up and suggested actions agreed upon to manage the conflicts of interest declared are summarized below:

- If members declare interests that are relevant to the meeting, the WHO Secretariat will note any potential conflict of interest and summarize these and then decide whether and to what extent they can participate in the guideline development.
- If the conflict is deemed to be significant, the WHO Secretariat will decide if the conflict necessitates exclusion of that person from participating in the guideline process or if their participation should be limited.
- These decisions are made on a case-by-case basis.

Below is a summary of the declared conflicts of interest and how these were managed.

A. GDG MEMBERS

GDG Members with no relevant interests declared on the DOI form and no relevant interests found in the CV

1. **Abdullah Al-Khathami**
   Ministry of Health, Riyadh, Saudia Arabia.
2. **Corrado Barbui**
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Jacqueline Curtis
University of New South Wales (UNSW), Sydney, Australia.

Dr Curtis received grants for research activities (three current grants amounting to a total of USD310,400 and three previous grants amounting to a total of USD16,600) from UNSW, New South Wales (NSW) government, commonwealth Bank of Australia and Prince of Wales Hospital, Sydney Foundation Patient Care Grant. She has been an expert advisor to the Orygen Youth Health (OYH) Research Centre, Melbourne for which she received USD440 remuneration in 2014. The OYH is part of the public mental health system in Melbourne, Australia, and sees young people aged 15 to 24, with a focus on early intervention and youth specific approaches. She also received honoraria for speaking at various scientific fora amounting to a total of USD5900 between 2014 and 2016 from the Adelaide Clinic, Tokyo Metropolitan Institute if Medical Science, Lundbeck, Townsville and Cairns Mental Health Services and OYH.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect Dr Curtis's judgement in the development of the present guidelines. No further action was necessary.*

Gail L. Daumit
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Dr Gail Lois Daumit is a Professor at Johns Hopkins Medical Institutions, Maryland, USA. In her DOI, she noted that the Johns Hopkins University School of Medicine received four Federal grants for research projects in which she is the principal investigator, with total annual direct costs of USD 1.7 million.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Daumit's judgement in the development of the present guidelines. No further action was necessary.*

Christopher Dowrick
University of Liverpool, Institute of Psychology, Health and Society

Dr Dowrick declared in his DOI form that as Chair of the Working Party for Mental Health of the World Organization of Family Doctors (WONCA) he has overseen the production and publication of a set of guidance documents and training materials for family doctors on the topic related to these guidelines.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Dowrick's judgement in the development of the present guidelines. He is deemed to be participating in the guideline development process in an individual capacity and not representing any organization. No further action was necessary.*

Oye Gureje
Department of Psychiatry University College Hospital, Ibadan, Nigeria.

Professor Oye Gureje is Professor of Psychiatry and Director, WHO Collaborating Centre for Research and Training in Mental Health, Neuroscience, Drug and Alcohol Abuse, University of Ibadan, Nigeria. In his DOI, he noted that he received research support amounting to $2.5million from the National Institute of Mental Health for a current project to study collaborative shared care for people with SMD.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Professor Gureje's judgement in the development of the present guidelines. No further action was necessary.*

Martin Prince
King's College London, London, United Kingdom.

Professor Prince declared in his DOI form that he currently receives research support through a grant from the National Institute of Health Research (NIHR, UK) amounting to GBP 7 million over four years. Prof Prince is the PI and 20% of his salary costs are charged to the grant. The work focuses on health systems strengthening in sub Saharan Africa and one theme relates to the topic of these guidelines i.e. integrated primary healthcare for multimorbid conditions.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Professor Prince's judgement in the development of the present guidelines. No further action was necessary.*

David Shiers
Healthy Active Lives (HeAL), Manchester, United Kingdom.

Dr David Shiers has honorary appointment with the Greater Manchester Mental Health NHS Foundation Trust and University of Manchester. In his DOI, he noted that he received remuneration as consultant the National Health Service, Royal College of Psychiatrists, NICE and Health Services Executive, Ireland for activities related to the subject of the meeting or the work. He also noted that he has received, along with other partners, a total of GBP 3.2 million funding for 6 research projects from the National Institute of Health Research, UK.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Shiers's judgement in the development of the present guidelines. No further action was necessary.*

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Ayesha Motala
University of KwaZulu-Natal, South Africa

Dr Motala declared that as a public servant working in a government institute, she seeks sponsorships to meetings from various organizations, especially when her scientific abstracts are accepted for presentations. The sponsorships are merely for attending the meetings, with no obligation to the sponsoring companies.

Details of such sponsorship for which she received a total amount of $26,000:

4-8 December 2017: International Diabetes Federation(IDF) Congress, Abu Dhabi: Sanofi Aventis sponsorship for travel and Accommodation; 11-15 September 2017: European Association for the Study of Diabetes(EASD) Congress, Lisbon: Pfizer sponsorship for Travel and accommodation; 8-13 June 2018: American Diabetes Association (ADA), San Diego: Boehringer Ingelheim sponsorship for Travel and accommodation: a member of her collaborating scientific team presented a paper.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Motala's contribution as an external reviewer for these guidelines. No further action was necessary.*

Charlene Sunkel
Central Gauteng Mental Health Society, South Africa

Ms Sunkel is a service user group representative and declared that she has published in the World Psychiatry journal on premature mortality of people with SMD titled: "A service users perspective" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5269497/

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Ms Sunkel's contribution as an external reviewer for these guidelines. No further action was necessary.*

Inka Weissbecker
International Medical Corps, Washington DC, USA.

Dr Weissbecker works for International Medical Corps (IMC) which is a humanitarian non-profit organization and has an interest in the subject of mental health and distress related to humanitarian crises (as IMC has various global projects integrating mental health and psychosocial support). She has also worked as a consultant in the field of mental health in the past (more than 10 years ago) including for WHO.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Weissbecker's contribution as an external reviewer for these guidelines. No further action was necessary.*

C. EXTERNAL PARTNERS

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Kavitha Kolappa
Harvard Medical School, Boston, USA

Dr Kolappa is part of the systematic review team for the development of these guidelines. Dr Kolappa declared that she received research support amounting to approximately USD 56,000 (USD 51,000 as stipend and USD 5000 for travel costs and purchase of computer) from the National Institutes of Health, USA. The period of this grant was for one year and ended in October 2017. Her area of study was the proposed relationship between social relationships, metabolic disease, and post-traumatic stress disorder.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Kolappa's contribution to the evidence review and synthesis process for the development of the present guidelines. As a member of the systematic review group she will be a technical resource and, therefore, will not participate in any of the closed sessions (voting or drafting final recommendations). No further action was necessary.*

Jayati Das-Munshi
King's College London, London, United Kingdom

Dr Das-Munshi is part of the systematic review team. In her DOI she noted that she is funded (amount GBP578198) by a Clinical Scientist Fellowship by a UK health charity, Health Foundation, in partnership with the Academy of Medical Sciences. She stated that the funder does not have any business or commercial interest in the work related to these guidelines and her research is independent of the funder's views.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Das-Munshi's contribution to the evidence review and synthesis process for the development of the present guidelines. As a member of the systematic review group she will be a technical resource and, therefore, will not participate in any of the closed sessions (voting or drafting final recommendations). No further action was necessary.*

Annex 3. Scoping questions

BACKGROUND QUESTIONS

1. Association of physical health conditions with SMD

What is the comorbidity between physical health conditions (NCDs and infectious diseases) and SMD?

What is the impact of physical health conditions on the morbidity and mortality of people with SMD?

PICO (POPULATION, INTERVENTION, COMPARISON, OUTCOME) QUESTIONS

2. Tobacco cessation

For people with SMD who use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) and/or non-pharmacological interventions effective to support tobacco cessation?

P: people with SMD who use tobacco

I: pharmacological interventions and/or non-pharmacological interventions:

- pharmacological interventions: including nicotine replacement therapy, bupropion, varenicline
- non-pharmacological interventions

C: care as usual and/or placebo

O:

- Critical
  - Tobacco cessation/abstinence rates
  - Tobacco consumption rates
  - Respiratory disease outcomes (COPD, asthma)
- Important
  - Frequency of adverse events/side-effects (including drug interactions)

3. Weight management

3.1 For people with SMD who are overweight or obese, are non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies effective to support weight reduction?

P: people with SMD who are overweight or obese

I: non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies:

- Non-pharmacological interventions: e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions
- Pharmacological interventions: weight-loss medication (e.g. orlistat)
- Pharmacological management strategies: e.g. switching antipsychotic medication

C: care as usual and/or placebo

O:

- Critical
  - Change in weight
  - Mean BMI (kg/m2) or change in BMI
- Important
  - Reduced sedentary behaviour
  - Maintenance of weight change/ Attenuation/prevention of weight gain
  - Frequency of adverse events/side-effects

3.2 For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

P: people with SMD who are at risk of becoming overweight or obese, e.g. people who have just started anti-psychotic medication

I: non-pharmacological interventions, e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions

C: care as usual

O:

- Critical
  - Change in weight
  - Mean BMI (kg/m2) or change in BMI
  - Maintenance of weight change
  - Attenuation/prevention of weight gain
- Important
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

4. Substance use disorders; drugs and/or alcohol

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological and/or non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

P: people with SMD and substance (drug and/or alcohol) use disorder

I: pharmacological and/or non-pharmacological interventions for substance use disorders:

- Pharmacological interventions
- Non-pharmacological interventions: e.g. motivational interviewing and/or CBT, psychoeducation, brief assessment interview, dual-focus interventions

C: care as usual / placebo or one treatment vs another

O:

- Critical
  - Level of consumption
  - Frequency of use
  - Abstinence
  - Relapse rates
- Important
  - Frequency of adverse events / side-effects

5. Cardiovascular disease / risk factors

5.1 For people with SMD and pre-existing cardiovascular disease, what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes

P: people with SMD and pre-existing cardiovascular disease: e.g. coronary heart disease, prior heart failure or stroke, cardiomyopathy, congenital heart disease, peripheral vascular disease

I: pharmacological and/or non-pharmacological interventions:

- pharmacological interventions
- non-pharmacological interventions

C: one treatment versus another or care as usual/placebo

O:

- Critical
  - Major adverse cardiovascular event (MACE) - includes cardiovascular death, myocardial infarction, stroke, heart failure, hospitalization, amputation
- Important
  - Frequency of adverse events/side-effects

5.2 For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

P: people with SMD and cardiovascular risk factors: a) high blood pressure (BP>140/90 mmHg; b) high lipid levels (e.g. cholesterol>200mg/dl or 5.2 mmol/l)

I: pharmacological and/or non-pharmacological interventions:

- pharmacological interventions: a) medication to control high blood pressure; b) medications for high lipid levels
- non-pharmacological interventions

C: one treatment versus another or care as usual/placebo

O:

- Critical
  - Adequacy of control of CVD risk factors (a. blood pressure <130/80mmHg; b. cholesterol <200mg/dl)
  - Cardiovascular disease incidence - MI, stroke, chronic cardiovascular disease
- Important
  - Frequency of adverse events/side-effects

6. Diabetes mellitus

For people with SMD and diabetes mellitus, what pharmacological and/or non-pharmacological interventions are effective to improve glycaemic control?

P: people with SMD and diabetes mellitus

I: pharmacological interventions and/or non-pharmacological interventions:

- pharmacological interventions: e.g. medication to treat diabetes
- non-pharmacological interventions: e.g. e.g. behavioural lifestyle interventions, cognitive behaviour therapy

C: one treatment versus another or care as usual

O:

- Critical
  - Fasting blood glucose <120mg/dl; post-prandial blood glucose<160mg/dl,
  - Glycosylated haemoglobin A1c (HbA1c<7 for people below 60 years and 7-8 for people above 60 years with other risk factors)
  - Diabetes complications – MACE, chronic kidney disease, diabetic retinopathy, diabetic neuropathy, hospitalization for infection
- Important
  - Frequency of adverse events / side-effects

7. HIV/AIDS

For people with SMD and HIV/AIDS, what pharmacological (i.e. ARV drugs, psychopharmacology) and nonpharmacological interventions are effective to support reduction in HIV-related outcomes?

P: people with SMD and HIV/AIDS

I:

- pharmacological interventions (ARV drugs, psychopharmacology)
- Nonpharmacological interventions

C: one treatment versus another or care as usual

O:

- Critical
  - HIV-related outcomes
- Important
  - Frequency of adverse events / side-effects

8. Other infectious diseases (Tuberculosis, Hepatitis B/C)

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and nonpharmacological (social, psychological) interventions are effective for treatment of infectious diseases (i.e. tuberculosis, hepatitis B, hepatitis C)?

P: people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C)

I:

- pharmacological interventions for infectious diseases
- Nonpharmacological (social, psychological) interventions for infectious diseases

C: one treatment versus another or care as usual

O:

- Critical
  - Infectious disease-related outcomes
- Important
  - Frequency of adverse events / side-effects

Annex 4. Background question: Association of physical health conditions with severe mental disorders

A. WHAT IS THE COMORBIDITY BETWEEN PHYSICAL HEALTH CONDITIONS (NCDS AND INFECTIOUS DISEASES) AND SMD?

A growing body of evidence has demonstrated the bi-directional relationships between SMD, including moderate to severe depression, bipolar disorder, as well as schizophrenia and other psychotic disorders, and physical health conditions including both non-communicable and infectious diseases.

SMD and non-communicable diseases (NCDs):

SMD and the major NCDs, including cardiovascular diseases, diabetes, respiratory illnesses, and cancers, are related in complex ways. From an epidemiological standpoint, mental disorder itself is a well-known risk factor for NCDs; its presence increases the chance that an individual will also suffer from one or more chronic illnesses. Overall, people with SMD have 1.53 times greater risk of cardiovascular disease and 1.85 times greater risk of death due to cardiovascular disease (Correll *et al.*, 2017). People with SMD, particularly those who have had multiple episodes of illness, also have higher rates of diabetes mellitus, with 1.85 times greater risk than the general population (Vancampfort *et al.*, 2016).

The reasons for the high co-morbidity between SMDs and NCDs have been extensively studied. People with SMD are more likely to engage in lifestyle behaviours that contribute to or exacerbate NCDs; that is, poor mental health is associated with the major modifiable risk factors for NCDs including tobacco use, harmful use of alcohol, unhealthy diets, and physical inactivity, which is elaborated further below. Additionally, pathophysiologically, persistent and SMD can affect and in turn, can be affected by stress-related NCDs (Watson *et al.*, 2017),(Kapczinski *et al.*, 2008; Nugent *et al.*, 2015). Furthermore, the iatrogenic effects of medicines used to treat SMDs are linked with increased risk of cardiometabolic diseases. Lastly, individuals with mental disorders are less likely to seek and receive screening and adequate treatment for NCDs, and symptoms may affect adherence to treatment as well as prognosis.

Tobacco consumption (Lasser *et al.*, 2000) is common amongst people with SMD and has been identified as a leading preventable cause of premature mortality in this population. Persons with schizophrenia and bipolar disorder are 5 times and 3 ½ times more likely to smoke currently than the general population, respectively (de Leon and Diaz, 2005),(Jackson *et al.*, 2015). ***Alcohol use disorders*** are also common amongst people with SMD, with one study using the national Danish registry finding the comorbidity of alcohol use disorder with schizo-phrenia, bipolar disorder, and depression to be approxi-mately 35%, 33%, and 23%, respectively. The comorbidity rates of ***all substance use disorders*** combined were even higher, with 48%, 40%, and 29% for schizophrenia, bipolar disorder, and de-pression, respectively (Jørgensen, Nordentoft and Hjorthøj, 2018).

Additionally, people with SMD are more likely to consume ***unhealthy diets*** and be ***physically inactive*** (Dipasquale *et al.*, 2013) (Jakobsen *et al.*, 2018) (Vancampfort *et al.*, 2017), which can lead to overweight, obesity, diabetes, and cardiovascular diseases. Overall, the risk of being ***overweight or obese*** as defined by a body mass index (BMI) of 25 or greater has been shown to be increased 3.4 fold for people with schizophrenia and 3.9 fold for people with bipolar disorder when compared with people without diagnoses of SMD (Gurpegui *et al.*, 2012). When considering obesity alone, as defined by a BMI of 30 or greater, the risk associated with schizophrenia and bipolar disorder jumps to 4.3 fold 4.6 fold, respectively (Gurpegui *et al.*, 2012).

Compounding the risks outlined above, the iatrogenic effects of psychotropic medications frequently used to treat the symptoms of SMD including antipsychotic medication (and to some extent, antidepressants and mood stabilizers) are linked with an increased risk of developing physical health conditions and associated complications (Correll *et al.*, 2015) (De Hert *et al.*, 2011) (Correll *et al.*, 2017). The use of antipsychotic medications has been associated with obesity, insulin resistance, diabetes, myocardial infarctions, atrial fibrillation, stroke, and death (Lieberman *et al.*, 2005) (Henderson *et al.*, 2005) (Chou *et al.*, 2017) (Sacchetti, Turrina and Valsecchi, 2010) (Yang *et al.*, 2018).

SMD and infectious diseases:

People with SMD are at greater risk than the general population for exposure to infectious diseases, including HIV, tuberculosis (TB) and chronic hepatitis. In the US, for example, persons with SMD were found to have a 10-fold higher prevalence of HIV (Hughes *et al.*, 2016). In a population-wide study in Sweden, persons with SMD when compared with the general population were found to have approximately 2.6 times greater risk of HIV infection, as well as 2.3 and 6.1 times greater risk of hepatitis B and C infections, respectively (Bauer-Staeb *et al.*, 2017). Further, one country-wide study in Taiwan revealed that persons with schizophrenia have a 1.5 times greater risk for tuberculosis infections than that of the rest of the population (Kuo *et al.*, 2013).

As is seen with NCDs, there is a bi-directionality of the association between SMD and infectious diseases. HIV virus and opportunistic infections associated with AIDS can cause neurological damage, while mental disorders can also arise as a side effect of antiretroviral treatment or from the stigma, stress and socio-economic predicaments associated with the infection and treatment process. There are widespread discriminatory attitudes and behaviours towards people with HIV, TB and Hepatitis B/C in the community where they reside, particularly in developing countries. The psychological distress associated with stigma and discrimination may also trigger or aggravate the symptoms of SMD in affected individuals.

B. WHAT IS THE IMPACT OF PHYSICAL HEALTH CONDITIONS ON THE MORBIDITY AND MORTALITY OF PEOPLE WITH SMD?

The mortality gap for people with SMD:

People with SMD, including moderate to severe depression, bipolar disorder, as well as schizophrenia and other psychotic disorders, have a 2-3 times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy (Liu *et al.*, 2017). Patients with bipolar disorder and schizophrenia have been shown to have higher rates of mortality in both high and low-income settings (Tsuang, Woolson and Fleming, 1980) (Capasso *et al.*, 2008) (Laursen, 2011) (Nielsen *et al.*, 2013) (Fekadu *et al.*, 2015) (Krupchanka *et al.*, 2018). One prospective cohort-study in Ethiopia, for example, found the overall standardized mortality ratio (SMR) of patients with SMD (schizophrenia, bipolar disorder, or severe depression) to be twice that of the general population, with schizophrenia associated with the highest risk (SMR three times that of the general population) (Fekadu *et al.*, 2015). Moreover, for schizophrenia in particular, the mortality gap appears to be widening over time (Saha, Chant and McGrath, 2007). While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to comorbid physical health conditions, both non-communicable and communicable (Liu *et al.*, 2017). Mortality in people with SMD is far higher in individuals with substance use disorders than in those without. It has been shown that alcohol use disorders as a comorbid condition to SMD doubled risk of all-cause mortality (Hjorthøj *et al.*, 2015).

The reasons for the mortality gap in people with SMD:

Numerous potential causes have been proposed for the increased mortality of patients with SMD including the well-known bidirectional relationship between mental disorders and other NCDs as elaborated above; differential exposure to risk factors driving the development of NCDs; iatrogenic effects of medications for SMD; increased risk for infectious diseases; comorbid substance use disorders; and inequitable access to health care services.

Equitable access to comprehensive health services remains out of reach for the majority of people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, spanning from promotion and prevention, screening, and treatment (De Hert *et al.*, 2011). Despite the elevated risks facing persons with SMD, screening for infectious illnesses such as HIV is poor (Mangurian *et al.*, 2017) (Senn and Carey, 2009). Screening for metabolic risk factors for persons with SMD, as well as those receiving antipsychotic medications also remains abysmal in low and high-income settings (Saloojee, Burns and Motala, 2014) (Morrato *et al.*, 2009) (Barnes *et al.*, 2007). Further, persons with SMD may not receive the life-saving care that they need. A large retrospective cohort analysis in the US found that when compared with people without mental disorder, people with schizophrenia were not even half as likely to receive cardiac catheterization after a heart attack (Druss *et al.*, 2000). It is crucial to address the disparities in health care access and provision for people with SMD. Recognizing the frequent comorbidity between mental and physical health conditions, specific recommendations addressing the physical conditions causing the increased morbidity and mortality of people with SMD are needed. In some instances, treatment recommendations for the general population may need to be adapted for people with SMD. Non-pharmacological interventions might warrant tailoring to account for cognitive, motivational, and social needs of people with SMD, and the benefits and risks of pharmacological interventions will need to be balanced against the potential side effects and drug-drug interactions between proposed interventions and psychotropic medications commonly used for SMD.

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Annex 5. Evidence review methodology

Comprehensive searches of major bibliographic databases were conducted in order to identify one or more systematic reviews that matched each of the outcomes for each of the PICO questions. The aim was to identify systematic reviews that were timely, of high quality and relevant to each of the PICO questions.

THE FOLLOWING PROCESS WAS EMPLOYED FOR THE SEARCHES:

1. Searched for systematic reviews (including meta-analyses) that were published in the last five years for each of the PICO questions. Guidelines from the last five years were also included, if these closely matched the population to whom the PICO question applies; any guidelines used needed to adhere to the WHO rules for guidelines. The searches were run in February 2018.

2. If no relevant high-quality systematic reviews were identified from the last five years for any of the PICO questions, the search was expanded to include systematic reviews from the last ten years for that PICO question. This was the case for the two PICO questions on HIV/AIDS and other infectious diseases; these searches were re-run in March 2018.

3. Where relevant, any guidelines that did not closely match the population to whom the PICO question applied (e.g. guidelines that apply to the general population) were used as indirect evidence.

4. For the PICO question on substance use disorder, based on the GDG's feedback during the GDG meeting in May 2018, the searches were expanded to include further search terms and were re-run in June 2018 (searching for systematic reviews from the last five years).

The following bibliographic databases were searched:

- Cochrane Library (including DARE) (title, abstract, keywords + mesh terms)
- PubMed/Medline (all fields)
- EMBASE (Ovid)
- PSYCINFO (anywhere)
- Epistemonikos (title/abstract)
- Global Health Library (title/abstract/subject)
- For those PICO questions where the search was expanded (see step 2 above), the National Guideline Clearing House was also searched.

After the searches were run using the search strategies listed on the pages below, titles and abstracts of all results were screened in Endnote; subsequently the full texts of those papers were reviewed that could not be excluded based on the title/abstract review.

GRADE EVIDENCE TABLES

All systematic reviews / meta-analyses that were identified as matching one of the PICO questions based on the search strategy described above were then assessed using the AMSTAR methodology[2], which evaluates the quality of systematic reviews using eleven criteria.

For each outcome of each PICOquestion, one or more systematic reviews were then selected to be used within the GRADE evidence tables for the PICO questions' evidence profiles. The following criteria were used when selecting which systematic review to use within the GRADE evidence tables:

- Published in the last five years, ideally three years (timeliness)
- High quality (i.e. at least six, but ideally more, of the eleven criteria of the AMSTAR scored positively)
- Closely relevant to the PICO
- Systematic reviews that dealt with SMD generally (rather than specific mental disorders) given preference
- Comprehensive systematic reviews given preference, where possible
- Cochrane reviews or other meta-analyses given preference, where possible/appropriate

The GRADE methodology involves rating the quality of the studies included in the systematic review according to study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Together with the effect sizes of studies, an overall 'certainty of evidence' is provided of either very low, low, moderate or high.

GRADE evidence tables were completed using the GRADEpro online tool[3]; the same criteria were used as for the mhGAP Intervention Guide when completing the GRADE evidence tables in terms of the assessment of the quality of studies (for risk of bias, inconsistency, indirectness, imprecision, and publication bias)[4].

[2] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology.* 2007; 7:10

[3] https://gradepro.org/

[4] See http://www.who.int/mental_health/mhgap/evidence/mhgap_guideline_process_2009.pdf

SEARCH STRATEGIES

Separate searches were performed for each of the seven PICO questions. Where PICO questions included both pharmacological and non-pharmacological interventions, searches were run separately for these.

The three search sets outlined below for each of the PICO questions were separated by an 'AND' when running the searches.

Filters were used in the bibliographic databases where possible to restrict the searches to systematic reviews and meta-analyses, as well as to humans. No further restrictions were employed, for example in terms of language (apart from the publication date, as mentioned above).

The 'Advanced Search' option was selected in bibliographic databases, where possible.

PICO QUESTION 2

For people with SMD who are use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) interventions effective to support tobacco cessation?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine/) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine/) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #3: pharmacological tobacco cessation interventions

(exp Smoking Cessation/ OR exp Smoking Reduction/ OR exp Tobacco Use Cessation/ OR exp Tobacco Use Cessation Products/ OR exp Bupropion/ OR exp Varenicline/ OR exp Nicotine Chewing Gum) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR (drug* OR medic*) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*)) OR

(bupropion OR varenicline OR "nicotine replacement therapy" OR "nicotine gum" OR "nicotine patch")

For people with SMD who are use tobacco, are non-pharmacological interventions effective to support tobacco cessation?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #3: non-pharmacological tobacco cessation interventions

(exp Smoking Cessation/ OR exp Smoking Reduction/ OR exp Tobacco Use Cessation/OR exp Tobacco Use Cessation Products/) OR

(exp Exercise Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

(“problem solving” OR psychoeducation OR couns*) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

PICO QUESTIONS 3.1 & 3.2

For people with SMD who are overweight or obese, are pharmacological interventions effective to support weight reduction?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

(“overweight” OR obes* OR “weight-related side-effects” OR “weight gain”)

Search #3: pharmacological interventions for weight reduction

(exp Obesity Management/ OR exp Anti-Obesity Agents/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((weight OR BMI OR “body mass*” OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR (“weight gain” AND (prevent* OR manag*)) OR

(orlistat OR “appetite suppressant*”)

For people with SMD who are overweight or obese, are pharmacological management strategies effective to support weight reduction?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

("overweight" OR obes* OR "weight-related side-effects" OR "weight gain")

Search #3: pharmacological interventions for weight reduction

(exp Obesity Management/ OR exp Anti-Obesity Agents/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((weight OR BMI OR "body mass*" OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

(switch* AND (medic* OR drug*))

For people with SMD who are overweight or obese, are non-pharmacological interventions effective to support weight reduction?

For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

("overweight" OR obes* OR "weight-related side-effects" OR "weight gain")

Search #3: non-pharmacological intervention for weight reduction and prevention

(exp Obesity Management/ OR exp Nutrition Therapy/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/ OR exp Health Promotion/ OR exp Diet/ OR exp Risk Reduction Behaviour/ OR Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/) OR

(exp Exercise Therapy/OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

(exp Preventive Health Services/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

(problem solving OR psychoeducation OR couns*) OR

((weight OR BMI OR body mass* OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR (weight gain AND (prevent* OR manag*)) OR

(diet* OR nutrition* OR exercis* OR sport* OR physical activit* OR health promot* OR self-monit* OR calor* OR healthy eating OR food intake)

PICO QUESTIONS 4

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Substance use disorder

(exp Narcotics/ OR exp Substance-Related Disorders/ OR exp Alcoholism/ OR exp Alcoholics/ OR exp Alcohol Related-Disorders/ OR exp Drug Users/ OR exp Drug Misuse/ OR exp Street Drugs/ OR exp Nonprescription Drugs/ OR exp Drug-Seeking Behaviour/ OR exp substance abuse, intravenous/) OR

("drug abuse" OR "drug addict*" OR "drug depend*” OR "drug withdrawal" OR "drug misuse") OR

("addictive disease*" OR "addictive disorder*" OR addiction OR addictive OR "substance abuse" OR “substance misuse” OR "withdrawal syndrome" OR psychoactive*) OR

("alcoholic patient*" OR "alcoholic subject*" OR alcoholism OR "alcohol depend*" OR "fetal alcohol*" OR "prenatal alcohol*" OR "chronic ethanol*" OR "chronic* alcohol*" OR "alcohol withdrawal" OR "ethanol withdrawal" OR “excessive alcohol consumption” OR “alcohol use disorder” OR “alcohol misuse” OR “alcohol abuse”) OR

((cocaine OR heroin OR cannabis OR marijuana OR mdma OR methylenedioxymethamphetamin* OR ecstasy OR morphine* OR amphetamin* OR methamphetamin* OR opioid* OR opiat* OR “prescription drug*” OR “illegal drug*” OR “illicit drug*" OR “street drug” OR benzodiazepin* OR tranquiliz* OR narcot* OR methadone OR fentanyl) AND (abuse OR misuse OR depend* OR addict* OR withdrawal OR overdose OR intoxication OR “harmful use”)) OR

(“injecting drug use” OR IDU$1 OR IVDU$1 OR PWID$1 OR “injecting drug” OR “intravenous drug” OR “injecting substance” OR “intravenous substance”)

Search #3: pharmacological interventions for substance use disorders

(exp Substance Abuse Treatment Centers/ OR exp Alcohol Abstinence/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

(exp buprenorphine/ OR exp methadone/ OR exp opiate substitution treatment/ OR exp buprenorphine, naloxone drug combination/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR (drug* OR medic*) OR

(methadone OR buprenorphine OR naloxone OR naltrexone OR disulfiram OR nalmefene OR thiamine OR clonidine OR lofexidine OR acamprosate OR baclofen) OR

("opioid agonist maintenance treatment" OR OST OR MMT OR BMT OR "opioid substitution treatment" OR "methadone" OR "methadone maintenance" OR "buprenorphine" OR "buprenorphine maintenance" OR "opioid replacement")

For people with SMD and substance (drug and/or alcohol) use disorder, are non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Substance use disorder

(exp Narcotics/ OR exp Substance-Related Disorders/ OR exp Alcoholism/ OR exp Alcoholics/ OR exp Alcohol Related-Disorders/ OR exp Drug Users/ OR exp Drug Misuse/ OR exp Street Drugs/ OR exp Nonprescription Drugs/ OR exp Drug-Seeking Behaviour/ OR exp substance abuse, intravenous/) OR

("drug abuse" OR "drug addict*" OR "drug depend*" OR "drug withdrawal" OR "drug misuse") OR

("addictive disease*" OR "addictive disorder*" OR addiction OR addictive OR "substance abuse" OR "substance misuse" OR "withdrawal syndrome" OR psychoactive*) OR

("alcoholic patient*" OR "alcoholic subject*" OR alcoholism OR "alcohol depend*" OR "fetal alcohol*" OR "prenatal alcohol*" OR "chronic ethanol*" OR "chronic* alcohol*" OR "alcohol withdrawal" OR "ethanol withdrawal" OR "excessive alcohol consumption" OR "alcohol use disorder" OR "alcohol misuse" OR "alcohol abuse") OR

((cocaine OR heroin OR cannabis OR marijuana OR mdma OR methylenedioxymethamphetamin* OR ecstasy OR morphine* OR amphetamin* OR methamphetamin* OR opioid* OR opiat* OR "prescription drug*" OR "illegal drug*" OR "illicit drug*" OR "street drug" OR benzodiazepin* OR tranquiliz* OR narcot* OR methadone OR fentanyl) AND (abuse OR misuse OR depend* OR addict* OR withdrawal OR overdose OR intoxication OR "harmful use")) OR

("injecting drug use" OR IDU$1 OR IVDU$1 OR PWID$1 OR "injecting drug" OR "intravenous drug" OR "injecting substance" OR "intravenous substance")

Search #3: non-pharmacological interventions for substance use disorders

(exp Substance Abuse Treatment Centers/ OR exp Alcohol Abstinence/ OR exp Needle-Exchange Programs/) OR

(exp Exercise Therapy/ OR exp Occupational Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/ OR exp harm reduction/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns*) OR

("motivational interviewing" OR "motivational enhancement therapy" OR MET OR CBT OR "cognitive behavioural therapy" OR "cognitive behavioural therapy" OR "brief assessment interview" OR "contingency management" OR "social skills training" OR "relapse prevention" OR "case management" OR "assertive community treatment" OR "family interventions") OR

(SBIRT OR "screening and brief interventions" OR outreach OR "residential programmes" OR "recovery management" OR "mutual self-help group" OR "Alcoholic Anonymous" OR "Narcotic Anonymous") OR

("harm reduction" OR NSP$1 OR NSEP$1 OR "needle syringe program$" OR "needle syringe exchange program$" OR "needle exchange$1" OR "syringe exchange $1")

PICO QUESTIONS 5.1 AND 5.2

For people with SMD and pre-existing cardiovascular disease, what pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: cardiovascular disease / risk factors

(exp Cardiovascular Diseases/) OR

("heart disease" OR "heart attack*" OR stroke* OR "myocardial infarction" OR "transient ischemic attack" OR "cerebrovascular disease" OR "congestive heart failure" OR "vascular disease") OR

("cardiovascular risk*" OR ((high OR abnormal OR elevat*) AND ("blood pressure" OR cholesterol OR "blood glucose")))

Search #3: pharmacological interventions for cardiovascular disease/risk

(exp Cardiac Rehabilitation/ OR exp Risk Reduction Behaviour/ OR exp Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

(exp Preventive Health Services/) OR

(switch* AND (medic* OR drug*))

For people with SMD and pre-existing cardiovascular disease, what non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: cardiovascular disease / risk factors

(exp Cardiovascular Diseases/) OR

("heart disease" OR "heart attack* OR stroke* OR "myocardial infarction" OR "transient ischemic attack" OR "cerebrovascular disease" OR "congestive heart failure" OR "vascular disease") OR

("cardiovascular risk*" OR (("high OR abnormal OR elevat*) AND ("blood pressure" OR cholesterol OR "blood glucose")))

Search #3: non-pharmacological interventions for cardiovascular disease/risk

(exp Cardiac Rehabilitation/ OR exp Risk Reduction Behaviour/ OR exp Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/OR exp Health Promotion/) OR

(exp Exercise Therapy/OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns*) OR

(exp Preventive Health Services/)

PICO QUESTION 6

For people with SMD and diabetes mellitus, what pharmacological interventions are effective to improve glycaemic control?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Diabetes mellitus

(exp Diabetes Mellitus/) OR

(diabet* OR NIDDM OR IDDM OR T2D* OR T1D*) OR

("non-insulin* depend*" OR "noninsulin* depend*" OR "insulin* depend*")

Search #3: pharmacological interventions for diabetes

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR service)) OR (drug* OR medic*) OR

((glucose* OR glycaem*) AND (treat* OR control* OR care OR servic* OR therap* OR interven* OR manag* OR monit*)) OR

(metformin OR sulphonylureas OR insulin OR thiazolidinediones) OR

((switch* AND (medic* OR drug*)) OR "appetite suppressant*" OR antiparkinsonian OR anticonvulsant* OR antidepressant* OR "health check*") OR

(weight AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

For people with SMD and diabetes mellitus, what non-pharmacological interventions are effective to improve glycaemic control?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Diabetes mellitus

(exp Diabetes Mellitus/) OR

(diabet* OR NIDDM OR IDDM OR T2D* OR T1D*) OR

("non-insulin* depend*" OR "noninsulin* depend*" OR "insulin* depend*")

Search #3: non-pharmacological interventions for diabetes

(exp Diet, Diabetic/) OR

(exp Exercise Therapy/ OR exp Occupational Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac* OR organisat* OR organizat*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns* OR education) OR

((glucose* OR glycaem*) AND (treat* OR control* OR care OR servic* OR therap* OR interven* OR manag* OR monit*)) OR

(diet* OR nutrition* OR exercis* OR "physical activity" OR "health promot*" OR self-monit* OR self-manag* OR self-care OR calor* OR "healthy eating" OR "healthy body weight" OR "food intake" OR "health check*") OR

(weight AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

PICO QUESTION 7

For people with SMD and HIV/AIDS, what pharmacological interventions (i.e. ART drugs) and non-pharmacological interventions are effective to support reduction in HIV-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: HIV/AIDS

(exp HIV/ OR exp Sexually Transmitted Diseases/ OR exp Lymphoma, AIDS-Related/ OR exp HIV Long-Term Survivors/ OR exp HIV Infections OR exp Acquired Immunodeficiency Syndrome/) OR

(HIV OR "human immunodeficiency syndrome" OR "human immunodeficiency virus" OR AIDS OR "acquired immunodeficiency syndrome")

Search #3: interventions for HIV/AIDS

(exp HIV Antigens/ OR exp Anti-HIV Agents/ OR exp Anti-Retroviral Agents/ OR exp Antiretroviral Therapy, Highly Active/ OR exp AIDS Vaccines/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((“anti-retroviral” OR ART) AND (drug* OR medic* OR intervent* OR therap* OR treat* OR care)) OR

(tenofovir OR TDF OR lamivudine OR 3TC OR emtricitabine OR FTC OR efavirenz OR EFV OR Abacavir

OR Zidovudine OR Nevirapine OR Atazanavir OR ritonavir OR Darunavir OR Lopinavir OR Dolutegravir OR Raltegravir)

PICO QUESTION 8

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and non-pharmacological interventions are effective for treatment of infectious diseases (e.g. tuberculosis, hepatitis B, hepatitis C)?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: infectious diseases (tuberculosis, hepatitis B/C)

(exp Hepatitis/ OR exp Hepatitis, Viral, Human/ OR exp Tuberculosis/ OR exp Hepatitis B/ OR exp Hepatitis B Virus/ OR exp Hepatitis C/) OR

(“hepatitis B” OR “hepatitis C” OR tuberculosis)

Search #3: interventions for infectious diseases

(exp Hepatitis B Vaccines/ OR exp Hepatitis B Antigens/ OR exp Hepatitis C Antigens/ OR exp Tuberculosis Vaccines/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

(vaccin* OR BCG OR treatment adherence OR treatment completion) OR

(Ethambutol OR Rifampicin OR Insoniazid OR Pyrazinamide OR Rifabutin OR Rifampicin OR Rifapentine OR Entecavir OR Tenofovir OR Sofosbuvir OR Simeprevir OR Daclatasvir OR Dasabuvir OR Ribavarin OR Pegylated interferon)

Drug-drug interactions search strategy

Drug-drug interaction searches were conducted between medicines relevant for each PICO question and medicines used for SMD. The following process was employed for the searches:

Medicines of interest were identified for each PICO question by referring to relevant sections of the 2017 WHO Model List of Essential Medicines (EML), as well as prior WHO Guidelines and WHO Mental Health Gap Action Programme Intervention Guide (mhGAP-IG) where applicable. Physical health medicines were limited in scope to those used on a routine basis, rather than emergently. Technical consultation was also sought with relevant departments of WHO. Pharmacological interventions recommended in the forthcoming guidelines were also included.

Medicines used for SMD were limited to those included in the WHO mhGAP-IG and/or the 2017 WHO EML. These will be expanded to include a wider range of medicines which may be used in different settings based on availability and costs. Since its inception in 1977, the WHO Model List of Essential Medicines has played an important role in identifying priority medications for major health conditions in countries of all income groups. Updated every two years, this list in many cases has been used as a gold standard for national health systems and non-governmental organization. Priority medications are selected based on efficacy, safety, and cost-effectiveness.

Searches between both lists (medicines relevant for each PICO question and medicines used for SMD) were run using the drug-drug interaction software Lexi-Interact. Lexi-Interact was chosen as it is commonly used in clinical practice and scored well on accuracy and comprehensiveness in a recent review comparing 5 drug-drug interaction engines[5]. Severity of drug-drug interactions (minor, moderate, major)) were reported in the Lexi-Interact database and have reported here.

Search results for each PICO question were summarized into a narrative synthesis within each Evidence Profile, as well as a table coded by drug-drug interaction severity with accompanying information in the annex.

[2] Sh Kheshti R, Aalipour M, Namazi S. "A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness." Journal of Research in Pharmacy Practice. 2016; 5: 257-263.

Annex 6. Drug – drug interactions

PICO 2: TOBACCO CESSATION

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Bupropion	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟢	🟢	🟢	🟢	🟡	🟢
Varenicline	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
NRT	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢

There are no known interactions between **NRT** or **varenicline** and medicines used for SMD.

BUPROPION:
There are multiple interactions between bupropion and medicines used for SMD, specifically involving elevated seizure risk and enzymatic inhibition/induction.

- **Amitriptyline:** Moderate interaction [elevated amitriptyline levels via CYP2D6 inhibition]. ADVICE: Consider other medications. If using, monitor clinically for signs of amitriptyline toxicity.
- **Fluoxetine:** Moderate interaction [elevated fluoxetine levels via CYP2D6 inhibition]. ADVICE: Monitor clinically for signs of fluoxetine toxicity and/or serotonin syndrome.
- **Haloperidol, risperidone, chlorpromazine, fluphenazine:** Moderate interaction [decreased seizure threshold]. Advise caution.
- **Clozapine:** Moderate interaction [decreased seizure threshold, elevated clozapine levels via CYP2D6 inhibition]. ADVICE: Monitor for signs of clozapine toxicity clinically and via testing of levels. Adjust clozapine dose accordingly.
- **Carbamazepine (CBZ):** Moderate interaction [lower levels of bupropion via CYP2B6 induction]. ADVICE: Monitor for clinical efficacy of bupropion.

PICO 3: WEIGHT MANAGEMENT

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Metformin	●	●	●	●	●	●	●	●	●	●	●	●	●

METFORMIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.

- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycemic control and adjust dosing of anti-diabetic medicine.

PICO 4: SUBSTANCE USE DISORDERS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Methadone	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟡	🟡	🔴	🟢	🟡	🔴
Buprenorphine	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟡	🟡	🔴	🟢	🔴	🔴

METHADONE:
There are multiple interactions between methadone and medicines for SMD, including increased risk for CNS depression* (sedation, confusion, decreased respiratory drive), QT-prolongation (methadone carries moderate risk), and serotonergic effects. Signs of serotonin syndrome include confusion, neuromuscular excitability, and dysautonomia.

- **Biperiden, trihexyphenidyl:** Moderate interaction. Elevated risk of side effects and toxicity of methadone including urinary retention and constipation [via anticholinergic activity]. ADVICE: Monitor for side effects.
- **Carbamazepine (CBZ):** Moderate interaction [reduced methadone levels and efficacy via CYP3A4 induction]. ADVICE: If using, monitor for reduced efficacy of methadone or opioid withdrawal symptoms.
- **Amitriptyline:** Major interaction [risk of CNS depression, serotonergic effects]. ADVICE: Avoid concurrent use if possible. If using, use lowest doses possible; monitor for clinical signs of CNS depression and signs of serotonin syndrome. Stop both medicines if serotonin syndrome suspected.
- **Fluoxetine:** Major interaction [high risk of QT prolongation, serotonergic effects]. ADVICE: Avoid using.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of CNS depression, risk of QT prolongation]. ADVICE: Avoid using if possible. If using, use lowest doses possible; monitor for clinical signs of CNS depression; monitor for QT-prolongation and arrhythmias on ECG.
- **Fluphenazine:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if possible. If using, use lowest doses possible and monitor for clinical signs of CNS depression.
- **Lithium:** Major interaction [serotonergic effects], Moderate interaction [risk of QT prolongation]. ADVICE: If using, monitor clinically for signs of serotonin syndrome. Stop both medicines if serotonin syndrome is suspected. Additionally, monitor for QT prolongation and arrhythmias on ECG if possible.
- **Diazepam:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if possible. If using, monitor for clinical signs of CNS depression.

BUPRENORPHINE:
There are multiple interactions between buprenorphine and medicines for SMD, including increased risk for CNS depression* (sedation, confusion, decreased respiratory drive), QT prolongation, and serotonergic effects (bupropion can increase the risk of serotonin toxicity or serotonin syndrome if used with medicines that have serotonergic effects). Signs of serotonin syndrome include confusion, neuromuscular excitability, and dysautonomia.

- **Biperiden, trihexyphenidyl:** Moderate interaction. Elevated risk of side effects and toxicity of buprenorphine including urinary retention and constipation [via anticholinergic activity]. ADVICE: Monitor for side effects.

- **Amitriptyline:** Major interaction [risk of CNS depression, serotonergic effects]. ADVICE: If using, consider decreasing amitriptyline and starting buprenorphine at a low dose; monitor for clinical signs of CNS depression. Additionally, monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected.

- **Fluoxetine:** Major interaction [serotonergic effects], Moderate interaction [risk of QT prolongation]. Fluoxetine confers high-risk for QT interval prolongation and buprenorphine may increase this risk, though the evidence is unclear. ADVICE: monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected. Monitor ECG if possible.

- **Haloperidol, risperidone, chlorpromazine, fluphenazine, clozapine, carbamazepine, diazepam:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if concerns for risk of buprenorphine misuse. If using, consider decreasing other sedating medicines and starting buprenorphine at a low dose; monitor for clinical signs of CNS depression.

- **Lithium:** Major interaction [serotonergic effects]. ADVICE: Monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected.

* Of note, the US FDA issued a safety announcement in 2017 regarding the use of methadone and buprenorphine with other sedating medications. While the risks of CNS sedation can be serious, they may be outweighed by the risk of other harms of untreated opioid use disorders. Thus, the US FDA does not recommend withholding opioid replacement therapy in the context of other sedating medications; cautious medication management is advised. United States Food and Drug Administration. Drug Safety and Availability - FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. 2017. https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm

PICO 5: CARDIOVASCULAR DISEASE

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Bisoprolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Atenolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Metoprolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Carvedilol	●	●	●	●	●	●	●	●	●	●	●	●	●
Glyceryl trinitrate	●	●	●	●	●	●	●	●	●	●	●	●	●
Isosorbide dinitrate	●	●	●	●	●	●	●	●	●	●	●	●	●
Verapamil	●	●	●	●	●	●	●	●	●	●	●	●	●
Digoxin	●	●	●	●	●	●	●	●	●	●	●	●	●
Amiodarone	●	●	●	●	●	●	●	●	●	●	●	●	●
Amlodipine	●	●	●	●	●	●	●	●	●	●	●	●	●
Enalapril	●	●	●	●	●	●	●	●	●	●	●	●	●
Hydrochlorothiazide	●	●	●	●	●	●	●	●	●	●	●	●	●
Losartan	●	●	●	●	●	●	●	●	●	●	●	●	●
Furosemide	●	●	●	●	●	●	●	●	●	●	●	●	●
Spironolactone	●	●	●	●	●	●	●	●	●	●	●	●	●
Aspirin	●	●	●	●	●	●	●	●	●	●	●	●	●
Clopidogrel	●	●	●	●	●	●	●	●	●	●	●	●	●
Simvastatin	●	●	●	●	●	●	●	●	●	●	●	●	●
Metformin	●	●	●	●	●	●	●	●	●	●	●	●	●

There are no known interactions between digoxin and medicines used for SMD.

BETA-BLOCKERS:

As a class, beta-blockers have significant interactions with multiple SMD medicines, most significantly the risk of hypotension or beta-blocker toxicity (including hypotension, bradycardia, and heart block/prolonged PR interval). There are some variations within this class.

- **Risperidone, chlorpromazine, fluphenazine, clozapine:** Moderate interaction for most beta-blockers [risk of hypotension] ADVICE: Monitor therapy.
- **Fluoxetine (with carvedilol and metoprolol only):** Moderate interaction with carvedilol, Major interaction with metoprolol. [Elevated levels of beta blocker via CYP2D6 inhibition] ADVICE: Consider alternative. If using, monitor for signs of beta blocker toxicity; adjust dosing accordingly.
- **Carbamazepine (with bisoprolol only):** Major interaction [reduced levels and efficacy of bisoprolol via CYP3A4 induction]. ADVICE: Consider alternative. If using, monitor for reduced efficacy of bisoprolol.

GLYCERYL TRINITRATE:

- **Amitriptyline, haloperidol, risperidone, chlorpromazine, fluphenazine, clozapine, biperiden, trihexyphenidyl:** Moderate interaction [reduced absorption of sublingual glyceryl trinitrate due to dry mouth from anticholinergic effects]. ADVICE: If dry mouth develops, utilize strategies such as artificial saliva and chewing gum

ISOSORBIDE DINITRATE:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [elevated risk of hypotension] ADVISE caution and monitor.
- **Carbamazepine:** Major interaction [reduced levels and efficacy of isosorbide dinitrate] ADVICE: Consider alternative.

VERAPAMIL:

Verapamil may elevate the levels of multiple medicines due to P-glycoprotein, CYP3A4, or CYP1A2 inhibition.

- **Haloperidol, risperidone, clozapine:** Moderate interaction [elevated levels of antipsychotic via CYP3A4, P-glyocoprotein, or CYP1A2 inhibition] ADVICE: Monitor for toxicity of antipsychotic
- **Chlorpromazine:** Moderate interaction [elevated risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Lithium:** Moderate interaction [increased risk of neurotoxicity from lithium; unclear effect on levels] ADVICE: Monitor clinically, as well as via laboratory levels
- **Diazepam:** Moderate interaction [increased levels of diazepam via CYP3A4 inhibition] ADVICE: Monitor for signs of diazepam toxicity
- **Carbamazepine (CBZ):** Major interaction [reduced levels and efficacy of verapamil via CYP3A4 induction, elevated levels of CBZ via CYP3A4 inhibition] ADVICE: Consider another mood stabilizer

AMIODARONE:

- **Fluoxetine, haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [QT prolongation] ADVICE: Avoid using
- **Amitriptyline, lithium:** Major interaction [QT prolongation] ADVICE: If able, avoid using. If using, monitor for QT-prolongation and arrythmias on ECG.
- **Carbamazepine:** Major interaction [reduced levels and efficacy of amiodarone] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of amiodarone.

AMLODIPINE:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Carbamazepine:** Major interaction [reduced levels and efficacy of amlodipine via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of amlodipine and adjust doses accordingly.

ENALAPRIL, LOSARTAN:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Lithium:** Moderate interaction with losartan, Major interaction with enalapril. [Elevated levels of lithium] ADVICE: Consider decreasing lithium when starting losartan or enalapril. Monitor for signs of lithium toxicity clinically and via laboratory testing.
- **Carbamazepine (with losartan only):** Major interaction [reduced levels and efficacy of losartan via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If used, monitor for reduced efficacy of losartan.

DIURETICS (HCTZ, FUROSEMIDE, SPIRONOLACTONE):

Diuretics have significant interactions with multiple SMD medicines, including the risk of hypotension.

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Amitriptyline, haloperidol, fluphenazine, biperiden, trihexyphenidyl, risperidone, chlorpromazine, clozapine (with HCTZ only):** Moderate interaction [increased levels of HCTZ due to effects on gut motility] ADVICE: Monitor for side effects of HCTZ
- **Fluoxetine, carbamazepine (with HCTZ only):** Moderate interaction [increased risk of hyponatremia] ADVICE: Monitor for clinical signs of hyponatremia including headache, dizziness, nausea, confusion, seizures
- **Lithium (with HCTZ only):** Moderate interaction [increased lithium levels] ADVICE: Consider decreasing lithium dose when HCTZ is started. Monitor for signs of lithium toxicity clinically and via laboratory testing.
- **Risperidone with furosemide only:** Major interaction [increased risk of mortality in patients with dementia] ADVICE: Consider another antipsychotic. If using, monitor carefully, especially hydration status.

ASPIRIN:

- **Amitriptyline, fluoxetine:** Major interaction [increased risk of bleeding, especially gastrointestinal bleeding] ADVICE: Monitor for signs of bleeding
- **Valproic acid:** [VPA] Moderate interaction [elevated levels of VPA] ADVICE: Monitor for toxicity of VPA clinically and via laboratory testing if possible

CLOPIDOGREL:

- **Fluoxetine:** Major interaction [reduced levels of active metabolite of clopidogrel via CYP2C19 inhibition] ADVICE: Consider another antidepressant. If using, monitor for reduced efficacy of clopidogrel.

SIMVASTATIN:

- **Risperidone:** Moderate interaction [increased risk of myopathy and rhabdomyolysis] ADVICE: Monitor clinically for any concerning symptoms
- **Carbamazepine:** Major interaction [reduced levels and efficacy of simvastatin via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of simvastatin.

METFORMIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

PICO 6: DIABETES

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Metformin	●	●	●	●	●	●	●	●	●	●	●	●	●
Gliclazide	●	●	●	●	●	●	●	●	●	●	●	●	●
Insulin	●	●	●	●	●	●	●	●	●	●	●	●	●

METFORMIN, INSULIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

GLICLAZIDE:

- **Amitriptyline, Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

PICO 7: HIV/AIDS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Dolutegravir	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢
Efavirenz	🟡	🔴	🔴	🔴	🔴	🟡	🔴	🟢	🟢	🟡	🟢	🔴	🟡
Emtricitabine	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Lamivudine	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Tenofovir disoproxil fumarate (TDF)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢

There are no known interactions between **emtricitabine, lamivudine**, or **tenofovir disoproxil fumarate (TDF)** and medicines used for SMD.

DOLUTEGRAVIR (DTG):

Major interaction with carbamazepine (CBZ).

- **CBZ** may reduce the level and efficacy of DTG. ADVICE: Double the dose of DTG if patient not on integrase inhibitors before. If resistance suspected to DTG (or similar drug in the same class), choose another mood stabilizer.

EFAVIRENZ:

There are multiple interactions between Efavirenz and medicines used for SMD, specifically involving the risk of QT interval prolongation, the risk of CNS depression (ex: sedation, confusion, decreased respiratory drive), and/or enzymatic induction.

- **Amitriptyline:** Moderate interaction [QT prolongation, risk of CNS depression]. ADVICE: If using, monitor for QT-prolongation and arrhythmias on ECG if possible and monitor for signs of CNS depression.
- **Lithium:** Moderate interaction [QT prolongation]. ADVICE: If using, monitor for QT-prolongation and arrhythmias on ECG if possible
- **Fluphenazine, Diazepam:** Moderate interaction [risk of CNS depression]. ADVICE: If using, monitor for signs of CNS depression.
- **Haloperidol, risperidone, chlorpromazine, and clozapine:** Major interaction [QT prolongation]. ADVICE: If able, avoid using efavirenz with these medicines. If using, monitor for QT-prolongation and arrythmias on ECG.
- **Fluoxetine:** Major interaction [high risk of QT prolongation]. ADVICE: Avoid using.
- **Carbamazepine:** Major interaction. Efavirenz and carbamazepine may reduce the levels (and efficacy) of each other. ADVICE: Avoid using.

* For details as to interactions between second-line and third-line antiretroviral and psychiatric medicines, please refer to (Annex 13: Key drug-drug interactions for antiretroviral drugs), which is available online at the following link: http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

PICO 8: TUBERCULOSIS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Isoniazid	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟡	🟢
Rifampin/ Rifampicin	🟡	🟡	🔴	🟡	🟢	🟢	🔴	🟢	🟢	🟢	🔴	🔴	🔴
Pyrazinamide	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Ethambutol	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Levofloxacin	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🟢	🟢
Cycloserine	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Bedaquiline	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🔴	🟢
Delamanid	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🔴	🟢
Linezolid	🔴	🔴	🟡	🟡	🟡	🟡	🟡	🟢	🟢	🔴	🟢	🔴	🟢

There are no known interactions between pyrazinamide, ethambutol, or cycloserine and medicines used for SMD.

ISONIAZID (INH):

- **Valproic acid:** Moderate interaction. INH can increase valproic acid levels. ADVICE: If using, monitor for valproic acid toxicity clinically and via laboratory testing of levels, if possible, especially when starting, stopping, or adjusting INH.
- **Carbamazepine (CBZ):** Moderate interaction. INH can increase CBZ levels and CBZ may increase the hepatotoxicity of INH. ADVICE: If using, monitor for clinical signs of CBZ toxicity and hepatotoxicity.

RIFAMPIN/RIFAMPICIN:

There are multiple interactions between rifampin and medicines used for SMD due to rifampin's ability to induce multiple enzymes (rifampin is a strong inducer of CYP3A4 and CYP2C9).

- **Amitriptyline:** Moderate interaction [reduced levels and efficacy of amitriptyline]. ADVICE: Monitor clinically for efficacy of amitriptyline.
- **Fluoxetine:** Moderate interaction [reduced levels and efficacy of fluoxetine]. Mechanism: CYP2C9 induction. ADVICE: Monitor clinically for efficacy of fluoxetine.
- **Risperidone:** Moderate interaction [reduced levels and efficacy of risperidone]. Mechanism: CYP3A4 induction. ADVICE: Monitor clinically for efficacy of risperidone and adjust dosing accordingly.
- **Haloperidol:** Major interaction [reduced levels and efficacy of haloperidol]. Mechanism: CYP3A4 induction. ADVICE: Consider another antipsychotic medication. If using, monitor for clinical efficacy of haloperidol and adjust dosing as needed.

- **Clozapine:** Major interaction [reduced levels and efficacy of clozapine]. Mechanism: CYP3A4 induction. ADVICE: Avoid using. If using, monitor for efficacy clinically and via clozapine levels and adjust dosing as needed.
- **Valproic acid (VPA):** Major interaction [reduced levels and efficacy of VPA]. ADVICE: Monitor for efficacy clinically and via VPA levels if possible, especially with dosing changes of rifampin; adjust VPA dosing accordingly.
- **Carbamazepine (CBZ):** Major interaction [reduced levels and efficacy of carbamazepine]. Mechanism: CYP3A4 induction. ADVICE: Consider another mood stabilizer. If using, monitor for clinical efficacy of CBZ and adjust dosing as needed.
- **Diazepam:** Major interaction [reduced levels and efficacy of diazepam]. Mechanism: CYP2C19 and CYP3A4 induction. ADVICE: Consider another medicine. If using, monitor for clinical efficacy of diazepam and adjust dosing as needed.

LEVOFLOXACIN:

There are multiple interactions between levofloxacin and medicines used for SMD due to increased risk for QT-prolongation (levofloxacin confers moderate risk).

- **Amitriptyline, fluoxetine, lithium:** Moderate interaction [increased risk for QT-prolongation]. ADVICE: Monitor for QT-prolongation and arrhythmias by ECG.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of QT prolongation]. ADVICE: Avoid using if possible. If using, monitor for QT-prolongation and arrhythmias on ECG.

BEDAQUILINE & DELAMANID:

There are multiple interactions between bedaquiline and delamanid with medicines used for SMD due to increased risk for QT-prolongation (both bedaquiline and delamanid confer moderate risk) and induction by CYP3A4.

- **Amitriptyline, fluoxetine, lithium:** Moderate interaction [increased risk for QT-prolongation]. ADVICE: Monitor for QT-prolongation and arrhythmias by ECG.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of QT prolongation]. ADVICE: Avoid using if possible. If using, monitor for QT-prolongation and arrhythmias on ECG.
- **Carbamazepine (CBZ):** Major interaction [reduced levels and effectiveness of bedaquiline or delamanid]. ADVICE: Consider another mood stabilizer.

LINEZOLID:

There are multiple interactions between linezolid and medicines used for SMD due to serotonergic effects, dopamine antagonism, and monoamine oxidase inhibition. Signs of serotonin syndrome include confusion, neuromuscular excitability (ex: myoclonus and hyperreflexia), and dysautonomia (ex: flushing, sweating, diarrhoea, high blood pressure and heart rate, and fever). Signs of neuroleptic malignant syndrome include confusion, muscle rigidity, and dysautonomia (ex: high fever, heart rate, or labile blood pressures).

- **Amitriptyline:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop amitriptyline at least two weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop amitriptyline and monitor clinically for signs of serotonin syndrome for at least two weeks after amitriptyline is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Fluoxetine:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop fluoxetine at least five weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop fluoxetine and monitor clinically for signs of serotonin syndrome for at least five weeks after fluoxetine is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Haloperidol, risperidone, chlorpromazine, fluphenazine:** Moderate interaction [serotonergic effects and dopamine antagonism, risk of serotonin syndrome and neuroleptic malignant syndrome]. ADVICE: Monitor clinically for signs of serotonin syndrome and neuroleptic malignant syndrome.
- **Clozapine:** Moderate interaction [serotonergic effects, dopamine antagonism, myelosuppressive effects, risk of serotonin syndrome and neuroleptic malignant syndrome, risk of neutropenia]. ADVICE: Monitor clinically for signs of serotonin syndrome and neuroleptic malignant syndrome. Monitor neutrophil count closely.
- **Lithium:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop lithium at least two weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop lithium and monitor clinically for signs of serotonin syndrome for at least two weeks after lithium is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Carbamazepine:** Major interaction [risk of increased monoamine oxidase inhibition by linezolid]. ADVICE: Do not use concurrently. Do not use carbamazepine for two weeks after stopping linezolid.

PICO 8: HEPATITIS B/C

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Tenofovir	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Entecavir	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Sofosbuvir	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢
Daclatasvir	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢
Ribavirin	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Ledipasvir	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢

There are no known interactions between **tenofovir**, **entecavir**, or **ribavirin** and medicines used for SMD.

SOFOSBUVIR:

- **Carbamazepine (CBZ):** Major interaction. Levels and efficacy of sofosbuvir may be reduced by intestinal P-glycoprotein inducers. CBZ may or may not be an inducer of intestinal P-glycoprotein; this effect is unclear. ADVICE: Do not use.

DACLATASVIR:

- **Risperidone:** Moderate interaction. Daclatasvir may increase levels of risperidone via P-glycoprotein/ABCB1 inhibition. ADVICE: Monitor for risperidone toxicity and adjust dose accordingly.
- **Carbamazepine (CBZ):** Major interaction. CBZ may reduce the levels and efficacy of daclatasvir via CYP3A4 induction. ADVICE: Do not use.

LEDIPASVIR:

- **Risperidone:** Moderate interaction. Ledipasvir may increase levels of risperidone via P-glycoprotein/ABCB1 inhibition. ADVICE: Monitor for risperidone toxicity and adjust dose accordingly.
- **Carbamazepine (CBZ):** Major interaction. Levels and efficacy of ledipasvir may be reduced by intestinal P-glycoprotein inducers. CBZ may or may not be an inducer of intestinal P-glycoprotein; this effect is unclear. ADVICE: Do not use.

Glossary

Bipolar disorder:
A person with bipolar disorder experiences episodes in which their mood and activity levels are significantly disturbed. They may experience periods of elevated mood and increased energy and activity (mania), as well as periods of low mood and decreased energy and activity (depression).

Collaborative care:
A model of care in which physical and mental health services are integrated. It is a multi-professional approach to patient care with a structured management plan, scheduled patient follow□up, and enhanced inter□professional communication.

Cognitive behavioural therapy:
Cognitive behavioural therapy (CBT) aims to address negative feelings by understanding thoughts and behaviours that lead to these feelings. A CBT therapist helps a person identify distorted thoughts and maladaptive behaviours.

Contingency management therapy:
Contingency management therapy is a form of therapy that involves encouraging positive, desired behaviours through rewards. Examples of desired behaviours include participating in treatment and reducing harmful substance use. It is recommended as a form of therapy for persons with alcohol or drug use disorders.

Depression, moderate to severe:
A person with moderate to severe depression typically may experience low mood, loss of interest or pleasure in activities, or low energy for at least two weeks or more. Additional symptoms may include reduced concentration and attention, reduced self-esteem and self-confidence, excessive feelings of guilt or unworthiness, bleak or pessimistic views of the future, disturbed sleep, diminished appetite, or ideas or attempts of self-harm or suicide.

Fixed-dose combination:
A fixed-dose combinations (FDC) is a combination of two or more medications in one pill, the goal of which is to simplify medication regimens. FDCs have been shown to increase adherence, decrease prescribing mistakes, and streamline procurement.

Glycaemic control:
Refers to control of blood sugar levels in patients with diabetes mellitus.

GRADE methodology:
Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology is an internationally agreed upon standard for rating the quality of studies included in a systematic review according to study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Iatrogenic effects:
Refer to the unintended side effects or health consequences of prescribed medication or other healthcare interventions.

Motivational interviewing or motivational enhancement therapy:
Motivational interviewing or motivational enhancement therapy is a type of therapy that engages a person in a discussion about their behaviour and what they perceive as the benefits and harms of this behaviour, with the goal of supporting behaviour change.

Noncommunicable diseases:
Noncommunicable diseases (NCDs) encompass all diseases that are not infectious in origin. The term NCDs commonly refers to mental disorders, cardiovascular diseases, diabetes, respiratory illnesses, and cancers.

Obese:
Excess weight, defined by a body-mass-index (BMI) of greater than or equal to 25 and less than 30.

Overweight:
Excess weight, defined by a body-mass-index (BMI) of greater than or equal to 30.

Severe mental disorders:
A group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders

Schizophrenia:
Schizophrenia is a chronic psychotic disorder, which is characterized by distortions of thinking and/or perception. Schizophrenia may manifest by disorganized thinking, paranoia or suspiciousness, delusional beliefs, altered perceptions or hallucinations, limited range of emotions, and/or impaired functioning.

Social determinants of health:
Defined as the social circumstances across a lifetime in which people are born, raised, and live their lives. Inequitable distribution of resources impact these conditions and subsequently impact numerous health outcomes.

Universal health coverage:
Universal health coverage (UHC) is a principle by which all persons have access to essential health care without onerous out-of-pocket expenditures.

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EXHIBIT 14

Facing page: Michigan Medicine Human Data and Biospecimen Release Committee Rubric.

An asterisk indicates a National Institutes of Health definition. The Michigan Medicine Human Data and Biospecimen Release Committee includes faculty and staff with a broad range of patient-related, clinical, research, legal, ethical, conflict-of-interest, technical, and industry-partnership expertise. Biweekly meetings involving use of a standardized checklist have enabled review of 70 projects over the past 12 months (approximately 3 projects per meeting). Types of data and biospecimens and actions that are exempted from the review process include summary data statistics without any individual-level data elements; "send-out" data or biospecimens intended for processing only when there are no third-party claims to the samples or derivatives; data or biospecimens generated during a clinical trial governed by our explicit study-specific research consents; and sharing of data or biospecimens with state or federal agencies or other academic medical centers. HIPAA denotes the Health Insurance Portability and Accountability Act, IRB institutional review board, PI principal investigator, and U-M University of Michigan.

ary research, how to manage known limitations regarding written informed consent as an indicator of effective communication, and how to handle selection bias owing to disparities created by the recruitment and consent process. More research, dialogue, and participant engagement are needed to achieve the correct balance between risk to individual participants and benefit to medical centers and society.

Disclosure forms provided by the authors are available at NEJM.org.

From the Departments of Obstetrics and Gynecology (K.S.-B.), Pediatrics (R.H.), and Anesthesiology (S.K.), and the Office of Research (E.O.K.), Michigan Medicine, and the Institute for Healthcare Policy and Innovation (K.S.-B., S.K.) and the Center for Bioethics and Social Sciences in Medicine (K.S.-B.), University of Michigan, Ann Arbor.

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Flattening the Curve for Incarcerated Populations — Covid-19 in Jails and Prisons

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Because of policies of mass incarceration over the past four decades, the United States has incarcerated more people than any other country on Earth. As of the end of 2016, there were nearly 2.2 million people in U.S. prisons and jails.[1] People entering jails are among the most vulnerable in our society, and during incarceration, that vulnerability is exacerbated by restricted movement, confined spaces, and limited medical care. People caught up in the U.S. justice system have already been affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and improved preparation is essential to minimizing the impact of this pandemic on incarcerated persons, correctional staff, and surrounding communities.

Populations involved with the criminal justice system have an increased prevalence of infectious diseases such as HIV and hepatitis C virus (HCV) infections and tuberculosis. Disparities in social determinants of health affecting groups that are disproportionately likely to be incarcerated — racial minorities, persons who are unstably housed, persons with substance use disorders or mental illness — lead to greater concentrations of these illnesses in incarcerated populations. Yet implementation of interventions to address these conditions is often challenging in correctional settings owing to resource limitations and policy constraints. Therefore, comprehensive responses that straddle correctional facilities and the community often need to be devised.

For example, HCV, which is the most prevalent infectious disease in incarcerated populations, is most commonly spread through

injection drug use. Transmission can be reduced using measures known to reduce high-risk behaviors, such as opioid agonist therapy and syringe exchange. Although much of the country has yet to implement these strategies in correctional settings, managing transitions in care to and from the community and providing such services to people after incarceration has a large impact. Similarly, we have learned that controlling infections such as HIV and HCV in correctional settings can have positive effects both in these settings and on surrounding communities, as a form of treatment as prevention.

Highly transmissible novel respiratory pathogens pose a new challenge for incarcerated populations because of the ease with which they spread in congregate settings. Perhaps most relevant to the Covid-19 pandemic, the 2009 H1N1 influenza pandemic exposed the failure to include jails in planning efforts. By the spring of 2010, vaccine was plentiful, yet most small jails never received vaccine, despite the presence of high-risk persons, such as pregnant women, and the increased risk of transmission among unvaccinated persons who spent time detained in close proximity to one another.[2]

"Social distancing" is a strategy for reducing transmission and "flattening the curve" of cases entering the health care system. Although correctional facilities face risks similar to those of community health care systems, social distancing is extremely challenging in these settings. Furthermore, half of all incarcerated persons have at least one chronic disease,[3] and according to the U.S. Department of Justice, 81,600 are over the age of 60, factors that increase the risk of poor outcomes of infection. With limited ability to protect themselves and others by self-isolating, hundreds of thousands of susceptible people are at heightened risk for severe illness.

To date, the Federal Bureau of Prisons and certain states and municipalities have opted to suspend visitation by community members, limit visits by legal representatives, and reduce facility transfers for incarcerated persons. To reduce social isolation and maintain a degree of connectedness for incarcerated people, some correctional systems are providing teleconferencing services for personal and legal visits. Irrespective of these interventions, infected persons — including staff members — will continue to enter correctional settings. By March 14, some U.S. correctional staff members had tested positive for SARS-CoV-2, and the first Covid-19 diagnosis in a detained person was announced on March 16. A recent SARS-CoV-2 outbreak among cruise-ship passengers and crew in Yokohama, Japan, provides a warning about what could soon happen in correctional settings.[4]

To operationalize a response for incarcerated populations, three levels of preparedness need to be addressed: the virus should be delayed as much as possible from entering correctional settings; if it is already in circulation, it should be controlled; and jails and prisons should prepare to deal with a high burden of disease. The better the mitigation job done by legal, public health, and correctional health partnerships, the lighter the burden correctional facilities and their surrounding communities will bear. We have learned from other epidemics, such as the 1918 influenza pandemic, that nonpharmaceutical interventions are effective, but they have the greatest impact when implemented early.[5]

Therefore, we believe that we need to prepare now, by "decarcerating," or releasing, as many people as possible, focusing on those who are least likely to commit additional crimes, but also on the elderly and infirm; urging police and courts to immediately suspend arresting and sentencing people, as much as possible, for low-level crimes and misdemeanors; isolating and separating incarcerated persons who are infected and those who are under investigation for possible infection from the general prison population; hospitalizing those who are seriously ill; and identifying correctional staff and health care providers who became infected early and have recovered, who can help with custodial and care efforts once they have been cleared, since they may have some degree of immunity and severe staff shortages are likely.

All these interventions will help to flatten the curve of Covid-19 cases among incarcerated populations and limit the impact of transmission both inside correctional facilities and in the community after incarcerated people are released. Such measures will also reduce the burden on the correctional system in terms of stabilizing and transferring critically ill patients, as well as the burden on the community health care system to which such patients will be sent. Each person needlessly infected in a correctional setting who develops severe illness will be one too many.

Beyond federal, state, and local

action, we need to consider the impact of correctional facilities in the global context. The boundaries between communities and correctional institutions are porous, as are the borders between countries in the age of mass human travel. Despite security at nearly every nation's border, Covid-19 has appeared in practically all countries. We can't expect to find sturdier barriers between correctional institutions and their surrounding communities in any affected country. Thus far, we have witnessed a spectrum of epidemic responses from various countries when it comes to correctional institutions. Iran, for example, orchestrated the controlled release of more than 70,000 prisoners, which may help "bend the curve" of the Iranian epidemic. Conversely, failure to calm incarcerated populations in Italy led to widespread rioting in Italian prisons. Reports have also emerged of incarceration of exposed persons for violating quarantine, a practice that will exacerbate the very problem we are trying to mitigate. To respond to this global crisis, we need to consider prisons and jails as reservoirs that could lead to epidemic resurgence if the epidemic is not adequately addressed in these facilities everywhere.

As with general epidemic preparedness, the Covid-19 pandemic will teach us valuable lessons for preparedness in correctional settings. It will also invariably highlight the injustice and inequality in the United States that are magnified in the criminal justice system. As U.S. criminal justice reform continues to unfold, emerging communicable diseases and our ability to combat them need to be taken into account. To promote public health, we believe that efforts to decarcerate, which are already under way in some jurisdictions, need to be scaled up; and associated reductions of incarcerated populations should be sustained. The interrelation of correctional-system health and public health is a reality not only in the United States but around the world.

Disclosure forms provided by the authors are available at NEJM.org.

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Blood Ties

Eliana V. Hempel, M.D.

The expansive window of the ICU room looks out over a gorgeous Sunday sunset. The room is pristine and organized. Monitors beep reassuringly. An incentive spirometer and a paper menu rest — comically, given the situation — on the bedside table. Everything in the room is familiar to me; I'm a doctor.

I've known him a long time, but the disheveled man before me with the hunted look in his eyes seems unfamiliar. His handkerchief makes repeated trips from his mouth to his lap, and each time his look of horror at the increasing amount of bright red blood intensifies. He can barely breathe, let alone talk, and the metallic smell of blood mingles with the smell of raw fear.

The screen behind me suddenly starts to glow, and a face appears: the tele-ICU physician. Backup. Thank goodness. Maybe he'll have some ideas. I spring into calm-doctor mode. I've done this countless times, faced emergencies with a calm exterior even as I wracked my brain for differential diagnoses, last-ditch treatment plans, and comforting words for

EXHIBIT 15

Open Letter to ICE from Medical Professionals Regarding COVID-19

Acting Director Matthew T. Albence
U.S. Immigration and Customs Enforcement
500 12th St. SW
Washington, D.C. 20536

Dear Acting Director Albence,

As concerned clinicians, we are writing this letter to urge U.S. Immigration and Customs Enforcement (ICE) officials to release individuals and families from immigration detention while their legal cases are being processed to prevent the spread of COVID-19 and mitigate the harm of an outbreak.

In light of the rapid global outbreak of the coronavirus disease 2019 (COVID-19), we want to bring attention to the serious harms facing individuals in immigration detention facilities under the custody of ICE. Health and Human Services Secretary Azar declared a public health emergency on January 31, 2020. As of March 13, 2020, there have been over 132,000 confirmed cases worldwide with nearly 5,000 deaths.

Conditions of Detention Facilities

Detention facilities, like the jails and prisons in which they are housed, are designed to maximize control of the incarcerated population, not to minimize disease transmission or to efficiently deliver health care. This fact is compounded by often crowded and unsanitary conditions, poor ventilation, lack of adequate access to hygienic materials such as soap and water or hand sanitizers, poor nutrition, and failure to adhere to recognized standards for prevention, screening, and containment. The frequent transfer of individuals from one detention facility to another, and intake of newly detained individuals from the community further complicates the prevention and detection of infectious disease outbreaks. A timely response to reported and observed symptoms is needed to interrupt viral transmission yet delays in testing, diagnosis and access to care are systemic in ICE custody. Further, given the patchwork regulatory system, it is unclear whether ICE or the county and state health departments are responsible for ensuring public health oversight of facilities.

For these reasons, transmission of infectious diseases in jails and prisons is incredibly common, especially those transmitted by respiratory droplets. It is estimated that up to a quarter of the US prison population has been infected with tuberculosis[1], with a rate of active TB infection that is 6-10 times higher than the general population.[2] Flu outbreaks are regular occurrences in jails and prisons across the United States.[3],[4] Recent outbreaks of vaccine-preventable illnesses including mumps, influenza, and varicella have similarly spread throughout immigration detention facilities. From September of 2018 to August 2019, 5 cases of mumps ballooned to nearly 900 cases among staff and individuals detained in 57 facilities across 19 states, a number that represents about one third of the total cases in the entire US in that time frame.[5] With a mortality rate 10 times greater than the seasonal flu and a higher R0 (the

average number of individuals who can contract the disease from a single infected person)[6] than Ebola, an outbreak of COVID-19 in immigration detention facilities would be devastating.

Risks of a COVID-19 Outbreak in Detention

Emerging evidence about COVID-19 indicates that spread is mostly via respiratory droplets among close contacts[7] and through contact with contaminated surfaces or objects. Reports that the virus may be viable for hours in the air are particularly concerning.[8] Though people are most contagious when they are symptomatic, transmission has been documented in absence of symptoms. We have reached the point where community spread is occurring in the United States. The number of cases is growing exponentially, and health systems are already starting to be strained. Social distancing measures recommended by the Centers for Disease Control (CDC)[9] are nearly impossible in immigration detention and testing remains largely unavailable. In facilities that are already at maximum capacity large-scale quarantines may not be feasible. Isolation may be misused and place individuals at higher risk of neglect and death. COVID-19 threatens the well-being of detained individuals, as well as the corrections staff who shuttle between the community and detention facilities.

Given these facts, it is only a matter of time before we become aware of COVID-19 cases in an immigration detention system in which detainees live in close quarters, with subpar infection control measures in place, and whose population represents some of the most vulnerable. In this setting, we can expect spread of COVID-19 in a manner similar to that at the Life Care Center of Kirkland, Washington, at which over 50% of residents have tested positive for the virus and over 20% have died in the past month. Such an outbreak would further strain the community's health care system. Considering the extreme risk presented by these conditions in light of the global COVID-19 epidemic, it is impossible to ensure that detainees will be in a "safe, secure and humane environment," as ICE's own National Detention Standards state.

In about 16% of cases of COVID-19 illness is severe including pneumonia with respiratory failure, septic shock, multi organ failure, and even death. Some people are at higher risk of getting severely sick from this illness. This includes **older adults over 60** and people who have **serious chronic medical conditions like heart disease, liver disease, diabetes, lung disease, and who are immunocompromised**. There are currently no antiviral drugs licensed by the U.S. Food and Drug Administration (FDA) to treat COVID-19, or post-exposure prophylaxis to prevent infection once exposed.

As such, we strongly recommend that ICE implement community-based alternatives to detention to alleviate the mass overcrowding in detention facilities. Individuals and families, particularly the most vulnerable—the elderly, pregnant women, people with serious mental illness, and those at higher risk of complications— should be released while their legal cases are being processed to avoid preventable deaths and mitigate the harm from a COVID-19 outbreak.

*This letter was written by physician members of the New York Lawyers for the Public Interest Medical Providers Network and Doctors for Camp Closure.

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[6] The R0 is the reproduction number, defined as the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection.
[7] Close contact is defined as—
a) being within approximately 6 feet (2 meters) of a COVID-19 case for a prolonged period of time; close contact can occur while caring for, living with, visiting, or sharing a health care waiting area or room with a COVID-19 case
b) having direct contact with infectious secretions of a COVID-19 case (e.g., being coughed on)
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EXHIBIT 16

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Pandemic Influenza and Jail Facilities and Populations

Persons processed into and through jail facilities in the United States may be particularly vulnerable during an influenza pandemic. Among other concerns, public health and corrections officials need to consider flow issues, the high turnover and transitions between jails and the community, and the decentralized organization of jails. In this article, we examine some of the unique challenges jail facilities may face during an influenza pandemic and discuss issues that should be addressed to reduce the spread of illness and lessen the impact of an influenza pandemic on the jail population and their surrounding communities. (*Am J Public Health.* 2009;99: S339–S344. doi:10.2105/AJPH.2009.175174)

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AT YEAREND 2007, MORE than 7.3 million adults were under correctional supervision in prison, in jail, on probation, or on parole, accounting for about 3.2% of the adult population in the United States.[1] Prisons are confinement facilities run by state or federal correctional authorities and typically house sentenced felons. Jails are confinement facilities usually administered by local law enforcement agencies and typically house persons awaiting trial or sentencing or who have been convicted and sentenced to terms of less than one year. Probation is a nonconfinement sanction involving supervision in the community. Parole is supervision of offenders after release from prison. Of the adults under correctional supervision, thirty percent—or about 2.3 million—were held in prisons or jail facilities throughout the country. About 800 000 of the 2.3 million were held in the more than 3000 jail facilities nationwide. Although jails held fewer inmates than prisons at yearend 2007, over the course of the year jails had more than an estimated 13 million bookings.[2]

Persons held in correctional facilities in the United States have higher rates of infectious and chronic diseases, mental illness, substance dependency, and homelessness prior to jail booking, than the general public.[3] During an influenza pandemic, these health and socioeconomic issues would likely make jail inmates particularly vulnerable because of their compromised immune systems and possible diminished capacity to understand the importance of taking medication. In addition, the large number of jail facilities and high turnover of jail inmate populations would likely present challenges for managing the spread of infection into jails from surrounding communities and, equally important, from jails into communities.

Such possibilities suggest the need for jail facilities and public health officials to work together during the pandemic influenza planning process. However, the decentralized nature of the jail system in the United States complicates the planning process. In this article, we address characteristics

of jails that public health officials need to be aware of when planning for an influenza pandemic. These characteristics include

1. the number and varying size of jail facilities in United States,
2. the high turnover of jail populations,
3. the connection between jail facilities and their surrounding communities,
4. the capacity of jails as it pertains to the ability to handle infected inmates, and
5. the prevalence of and capacity to provide services for physical health, mental health, and substance abuse problems of inmates.

We used data and reports collected and compiled by the United States Bureau of Justice Statistics (BJS), a component of the United States Department of Justice that is dedicated to collecting, analyzing, publishing, and disseminating data on crime, criminal offenders, victims of crime, and the operations of justice systems at all levels of government. The BJS data provide the only nationally representative data on jails and jail inmates. Because of the number and variety of jail systems in the nation, this is an important issue, though often overlooked. We focused on those data relevant to pandemic planning, such as population characteristics, turnover, and comorbid medical conditions. In addition, we reviewed 2005–2009 pandemic influenza planning literature posted by the government (available at http://www.pandemicflu.gov).

LOCAL JAIL CHARACTERISTICS

The latest data available indicate that throughout the United States, more than 3200 jail facilities were distributed among 2860 jail jurisdictions.[4,5] Jail jurisdictions are locally—usually county—operated entities. The majority of jails are likely to be operated by a county Sheriff, though some are operated by county governments and a small number are operated by private corporations under contract from a county government. Some local governments have formed regional jails, facilities created to house inmates from several counties. Conversely, some large counties maintain more than one jail facility.

Although most counties have a jail, the jail inmate population is concentrated in large jurisdictions. At midyear 2008, there were about 786 000 inmates held in jails nationwide.[6] The roughly 1100 jails holding fewer than 50 inmates on an average day (38% of all jails nationwide) held only 3.0% of the jail inmate population. Conversely, the largest 170 jails, which averaged more than 1000 inmates per day, (and accounted for 6% of all jail jurisdictions nationwide) housed 52% of the nation's jail inmate population (Figure 1).

Regardless of size, most jails perform multiple roles in the community (see the box on page S342). Partly as a result of performing multiple roles, jails admit and release annually many more times the number of detainees than they hold on a given day. For example, during 2007 jails had an estimated 13 million bookings. These bookings did not represent unique individuals, however. The number booked during the 12 months ending June 30, 2007, was 17 times the size of the jail inmate population at midyear 2007.[2] Moreover, the high ratio of admissions to total jail populations indicates that the jail inmate population turns over rapidly. During the last week of June 2007, jail turnover nationwide—measured in terms of the total number admitted and released divided by the average population—was 63.5%. This turnover varies with jail size. During the last week of June 2007, smaller jails—those housing fewer than 50 inmates on average—turned over at more than 100%, whereas the turnover rate in the largest jails—housing more than 1000 inmates—was about 54%.[2]

The high turnover rate also implies that the average time spent in jails is comparatively short. Nationwide, the average time served in jails amounts to approximately 21 days.[6] By comparison, average time served in prisons is more than 2 years. In the largest jails, almost half of all inmates booked into them spend 2 or fewer days there. A BJS survey covering the largest 140 jails in 2004 found that approximately 46% of the inmates released from these jails during 2004 served fewer than 3 days, another 16% served 3 to 7 days, and 18% served between 1 week and 1 month. At the time of release, only 1% of those from the largest jails had served more than 1 year.[7] Also in these large jails, the number of admissions fluctuates monthly, indicating that there may be some seasonality to the turnover rate. For example, within the largest jails, monthly admissions from January 2003 to January 2004 fluctuated from a low of 308 582 in February to a high of 357 259 in August.[2]

In terms of managing the movements of inmates booked into their facilities, jail administrators have relatively little control over the flow of inmates entering their facilities or the rate at which they leave. Judges decide whom to detain prior to trial and whom to sentence to jail rather than prison. Detained inmates may make bail at any time and be released. Parole boards or probation officials determine which offenders to detain in jail while awaiting hearings to determine if there were violations of conditions of supervision. Offenders regularly move from community supervision into jail facilities and from jail facilities into community supervision. On any given day, half of the nation's jail population represents failure to comply with conditions under community supervision—not necessarily a new criminal act. For example, during 2004 approximately 219 000 parolees (up from 133 900 in 1990) and 330 000 probationers (up from 222 000 in 1990) failed to comply with the conditions imposed on them while under community supervision and were returned to incarceration, either in prison or in jail.[7]

Despite the volatility in jail population movements over time, jail capacity has expanded at about the same rate, or even slightly faster, than the increase in the number of inmates confined in jails. Nationwide at midyear 2008, the number of inmates held in jails amounted to 95% of rated capacity. Since 2002, jails nationwide have operated at between 93% and 95% of capacity, up slightly from 90% in 2001. Smaller jails—for example the roughly 1100 housing fewer than 50 inmates on average and holding 3% of the jail population nationwide—operated at 67.3% of capacity. The 350 largest jails—those housing more than 500 inmates on average and holding more than two thirds of jail inmates nationwide—operated at near 100% of capacity.[5]

Many of the inmates flowing through jails suffer from medical and mental health conditions. In

2002, more than one third (37%) of all jail inmates reported having a current medical problem. Some 14% of jail inmates reported multiple medical problems. The most frequently reported medical problems by jail inmates were chronic diseases. The most commonly reported medical problem was arthritis (13%), followed by hypertension (11%), asthma (10%), and heart problems (6%). Infectious diseases were reported less frequently; approximately 4.3% reported ever having had tuberculosis, 2.6% reported hepatitis, 1.3% reported HIV infection, and 0.9% reported an STD.[8,9]

Wilper et al. provide standardized estimates of the prevalence of common chronic conditions in the incarcerated population (both prison and jail) as a whole for the purposes of comparing the prevalence of these conditions with those found in the general population. For our article, comparisons to the general population are not as relevant as the overall percentage of jail inmates with conditions.[9]

In addition, an increasing number of persons held in jails are non-US citizens, many of whom may come from high-risk countries. At midyear 2007, about 39 000 jail inmates were non-US citizens, accounting for about 5% of the jail population. Since 2000, the number of non-US citizens being held in jails has increased by 40%, whereas the number of US citizens being held in jails increased 9%.

Substance abuse and mental health problems are more prevalent among jail inmates than are medical problems. Approximately 2 in 10 jail inmates reported a recent history of mental health problems, including a clinical diagnosis or treatment in the year before arrest or since admission, according to a BJS survey of jail inmates.[10] Further, a recent study by Steadman et al., in which clinical diagnostic instruments were used to determine past-month prevalence of serious mental illness among a sample of adult male and female jail inmates in 5 jails (2 in Maryland and 3 in New York), reported a prevalence of serious mental illness of 14.5% for males and of 31.0% for females.[8] In addition, many inmates exhibit symptoms of mental health disorders based on criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), as nearly two thirds (64%) of jail inmates reported either a recent history of a mental health problem or symptoms of a mental health disorder.

Among jail inmates in 2002, two thirds (68%) met the criteria for either dependence on or abuse of alcohol or other illegal substances. Over half (53%) of jail inmates were either dependent on or abusing drugs, and nearly one half (47%) were either dependent on or abusing alcohol.[12] These factors combined affect issues of consent and ability to follow hygiene and prevention guidelines for inmates.

A review of personal interviews with jail inmates showed that in 2002, nearly half (47%) said that staff checked them to see if they were sick, and 81% said staff asked them questions about their health or medical history at admission.[8,11] More than 4 in 10 jail inmates had a medical examination since admission. Of every 10 inmates, 6 had been tested for tuberculosis, and more than 2 in 10 had been tested for HIV. About 4 in 10 jail inmates with a then-current medical problem had seen a doctor.

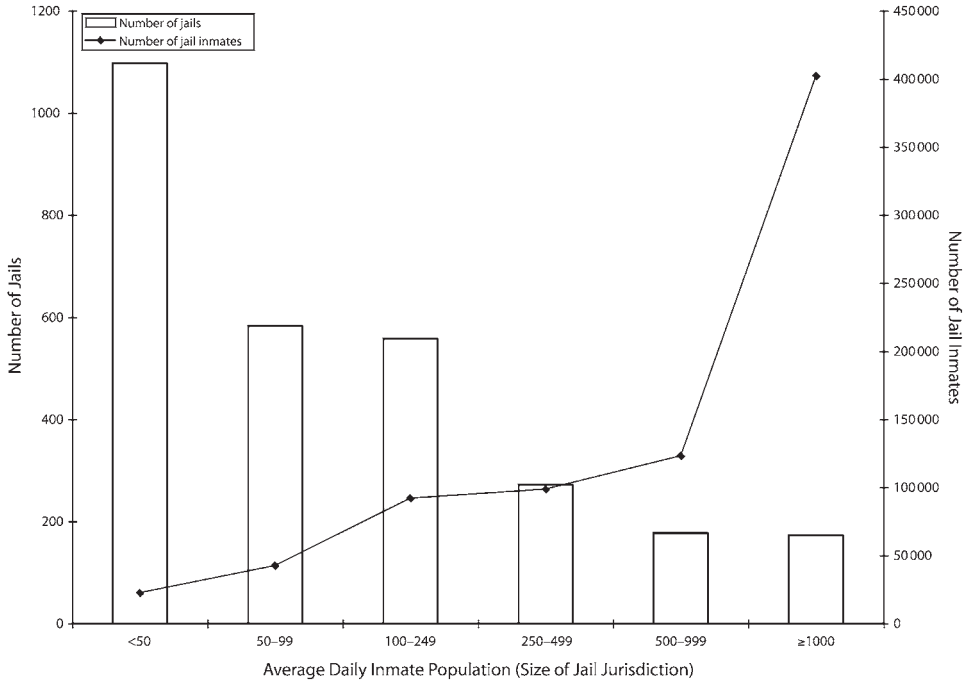

FIGURE 1—Number of jail inmates and jail jurisdictions, by size of jail jurisdiction: midyear 2007

IMPLICATIONS

The number and varying size of jails, the high turnover in jails, the connection between jails and the community, the capacity of jails, and the prevalence of and capacity to provide services for physical health, mental health, and substance abuse problems all have implications for preparing for pandemic influenza.

Although standards do exist for infection control programs in jails, only around 350 jails nationwide, less than 10% of all jails, are accredited by either or both major accrediting bodies with health standards (though this does not include states with internal accrediting processes). Good infection control practices inside jails may have an immediate effect on surrounding communities, and jails may be similarly affected by good infection control practices in communities. Yet given the fluidity of

Roles of Jails in Their Communities

Jails:

Receive individuals pending arraignment and hold them awaiting trial, conviction, or sentencing.
Readmit probation, parole, and bail bond violators and absconders.
Detain temporarily juveniles pending transfer to juvenile authorities.
Hold mentally ill persons pending their movement to appropriate mental health facilities.
Hold persons for the military, for protective custody, for contempt, and for the courts as witnesses.
Release convicted inmates to the community upon completion of sentence.
Transfer inmates to federal, state, or other authorities.
House inmates for federal, state or other authorities because of crowding in other facilities.

jail inmate populations, implementing infection control policies within jails may not be as easy as it sounds. In the largest jails, more than two thirds of the inmate population turns over within one week; in the smallest jails, the entire population turns over within one week. The short turnover times pose huge challenges in implementing infection control practices, particularly when jails are required to maintain security, transport detainees to court for hearings, and hold offenders for sentencing. The ongoing business of managing a jail poses challenges for administrators—adding procedures to control infection must take into account the roles and responsibilities of jails in the criminal justice system.

The pathway for transmission of pandemic influenza between jails and the community is a two-way street. Jails process millions of bookings per year. Infected individuals coming from the community may be housed with healthy inmates and will come into contact with correctional officers, which can spread infection throughout a facility. On release from jail, infected inmates can also spread infection into the community where they reside. Thus, a jail facility's pandemic influenza plan can directly affect not only the health of its inmate population but also the health of the surrounding community. For planning purposes, it is important to keep in mind that persons serving probation sentences are typically not eligible for health care in the community, in contrast to those held in jail. Further, while the Advisory Committee on Immunization Practices recommends providing influenza vaccine to all persons who want to reduce the risk of becoming ill with influenza or transmitting it to others, experiences with recent vaccine shortages raise questions about the priority that would be given to jail inmates and jail employees as vaccine recipients in the event of a pandemic.

Because jail capacity has expanded at approximately the rate of growth of the jail inmate population and it is not clear that a pandemic influenza outbreak would necessarily result in an increase in the number of persons held in jails, it is not obvious that expansion of jail capacity would be necessary during a pandemic. More important than the number of beds, per se, is the use of the bed. Important to the utilization of jail capacity for public health purposes is understanding the way in which people become sick with influenza. Influenza is thought to spread primarily from person to person when infected persons cough, sneeze, or talk, sending respiratory droplets into contact with susceptible persons. Research suggests that transmission might also occur when people touch contaminated objects and then touch their own nose, mouth or eyes with their hands.[13]

In the absence of a widely available pandemic influenza vaccine, corrections authorities could be constrained to recommend nonpharmaceutical interventions to reduce contact between people and to limit potential transmission. Planners would then need to consider developing infection control plans that specify needed reallocation of space and regrouping of inmates (possibly designated quarantine areas and treatment areas for those infected). If space and resources for delivery of medical treatment cannot be allocated, planners must think about security and staffing issues that could arise from the need for inmates to be transferred to hospitals. A primary function of jails is to transport inmates to court for appearances and back to jail, and jail administrators maintain security within facilities while operating these transport functions. However, in the event of an outbreak that resulted in a large increase in the number of inmates transferred to hospitals in addition to courts, jail managers will have to plan for the effects of additional transport to hospitals. Potentially, if expansion of jail capacity is needed, it may be expansion of the number of correctional officers to handle increased demands for transporting inmates and to avoid leaving facilities understaffed. The infection control planners should fully explore infection control measures that jails, employees, and inmates can take to prevent spread of influenza-like illness while still allowing the correctional facility to protect the community from offenders and ensuring the rule of law.

The data on morbidity in jails indicate that jail inmate populations contain many individuals with a compromised immune system. This factor may facilitate the spread of infection. Although jails are able to provide limited medical care, their capacity for screening for medical and mental health problems appears to be greater than their capacity to provide care. Planning for a pandemic outbreak should consider the health screening role for jails. One approach would be to develop new instruments for screening and to use public health resources to assist in training and implementing screening procedures. But implementing strategies to prevent the possible spread of infection may be difficult to put into practice unless a jail facility is able to screen and group its inmates according to infection status. Planners should consider developing and then exercising a workable, realistic plan to screen inmates and staff for influenza[14] using resources likely available during a pandemic.

Inmates with mental illness pose additional challenges for pandemic planning; even if inmates are screened and directed to resources in the community, health services will likely become overburdened

during a pandemic. Thus, any existing scarcity of mental health facilities in the community and any existing scarcity of access to necessary medications to control mental health illnesses may become more pronounced. This projected strain on health services poses a special challenge that planners need to address.

OTHER CONSIDERATIONS FOR PLANNING FOR PANDEMIC INFLUENZA IN JAILS

As corrections and public health officials align pandemic flu planning efforts with those of federal, state, local, public health, law enforcement, judiciary, and emergency management agencies, it is likely that their efforts would diminish the impact of a pandemic on correctional facilities and surrounding communities. The Department of Health and Human Services (HHS) provides a related and detailed pandemic planning checklist for correctional facilities at http://www.pandemicflu.gov/plan/workplaceplanning/correctionchecklist.pdf. Apart from drafting a plan, planners need to discuss their own missions and describe how they anticipate other agencies will respond during a pandemic. The Public Health/Law Enforcement Emergency Preparedness Workgroup (led by the Centers for Disease Control and Prevention and the Department of Justice) reported in July 2008 that law enforcement agencies and public health agencies should be aware of communication gaps that potentially exist between them. One example is that in the past, some agencies have mentioned other agencies in their plans and have made misguided assumptions about what actions those other agencies would implement. Another potential communication gap to address relates to the definition of key words such as "surveillance," which can have vastly different meanings between agencies; thus in advance of a pandemic, the group should ideally talk through and define words that have multiple meanings.[15]

An unresolved issue for planning is deciding which entities have responsibility for containing the spread of an influenza outbreak. One view is that testing and response should occur in jails and that the operations should be managed by jail officials. Another view is that public health officials should be primarily responsible for managing health concerns, including containing the spread of infection during a pandemic outbreak, whether done in jail facilities or in other locations in the community. Planning for pandemic influenza must address these issues of responsibility and delivery of services.

The Advisory Committee on Immunization Practices recommends providing influenza vaccine to all persons who want to reduce the risk of becoming ill with influenza or of transmitting it to others. The committee further advises an emphasis on providing routine vaccinations annually to certain groups at higher risk for influenza infection or complications, including all persons 50 years or older and other adults who are at risk for medical complications from influenza or who are more likely to require medical care.[13] The data on morbidity in jails indicate that jail inmate populations contain many persons with current medical problems. For planning purposes, when a pandemic influenza vaccine becomes widely available, each jail may want to compare the aforementioned Advisory Committee on Immunization Practices recommendations with their own inmate populations to see what percentage of the population would be most appropriate to vaccinate and in what order. In addition, given the high turnover in jail population and contact and interaction that correctional officers have with inmates, priority should be given to jail employees to minimize the spread of infection among them, which could in turn compromise prison security.

To ensure that jails can successfully carry out their missions during a pandemic, jail jurisdictions should plan for the likely absence of their employees due to the employee's illness or a family member's illness while at the same time working to protect employee health and to prevent spread of infection. Issues related to leave policies, health insurance, cross-training, and possible reduced work force are ideally addressed in advance of a pandemic. In addition to directing employees, planners should work to consider all the others who operate and who process through jails and who therefore during a pandemic could potentially be exposed to influenza.

We must begin to think of jails not as separate from the community but as collections of workers and detained persons who have a constant connection with the surrounding community. Thus, the boundary between jails and the community is relatively porous—what affects those behind the bars also affects those on the outside.

During a pandemic, jail medical services will likely be insufficient to treat large numbers of sick inmates; further, local hospitals may be overburdened and unable to admit inmates who are seriously ill with influenza.[16] Preventing the spread of pandemic influenza illness among inmates is therefore key to preserving the larger community's health. ■

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Contributors

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EXHIBIT 17

Sartorius N, Holt RIG, Maj M (eds): Comorbidity of Mental and Physical Disorders.
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Anxiety and Related Disorders and Physical Illness

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Abstract

Anxiety and related disorders are the most prevalent mental disorders in the general population. There is a strong bidirectional association between anxiety and related disorders and co-occurring general medical conditions. The co-occurrence of anxiety and related disorders and general medical conditions is associated with significant impairment, morbidity and economic costs. At the same time, recognition of anxiety and related disorders in people with medical illness may be challenging when comorbid with physical illness due in part to overlap in symptomatology. Furthermore, there is a relatively limited evidence base of randomized controlled trials in this population. Additional work is needed to improve screening for anxiety and related disorders in medical illness, to enhance diagnosis and assessment, and to optimize treatment.

Anxiety disorders, obsessive-compulsive and related disorders, and trauma- and stressor-related disorders are the most prevalent psychiatric disorders in the general population [1, 2], with generalized anxiety disorder the most common anxiety disorder in primary care populations [3]. Indeed, these anxiety and related disorders occur frequently with a range of general medical disorders [4, 5], including gastrointestinal disease [6], pulmonary disease [7, 8], cardiovascular disease [9], endocrine disorders [10], dermatological disorders [11] and cancer [12], as well as neuropsychiatric disorders such as chronic pain [13, 14], migraines [15], dementia [16] and Parkinson's disease [17]. In this chapter we review the epidemiology of comorbid anxiety and related disorders and physical illness, the growing evidence of a bidirectional relationship between these sets of conditions [18] and relevant randomized controlled trials in this area.

Epidemiology

Anxiety and related disorders are the most common psychiatric disorders worldwide, with a 12-month prevalence worldwide of between 4 and 20% [2]. The onset of anxiety and related disorders usually happens in childhood or adolescence, with many individuals first presenting with physical symptoms in primary care settings

Table 1. Common medical conditions associated with anxiety

Endocrine disorders	diabetes mellitus [32], thyroid disease [10], catecholamine-secreting pheochromocytoma
Gastrointestinal disorders	peptic ulcers [27], celiac disease [33], irritable bowel syndrome [26]
Musculoskeletal disorders	fibromyalgia/chronic fatigue syndrome [34], arthritis [35]
Neurological disorders	migraines [15], epilepsy, neurodegenerative illness [17]
Cardiorespiratory disease	asthma [30], angina [25], chronic obstructive pulmonary disease [7], mitral valve prolapse [36], cystic fibrosis [8], obesity [24, 37, 38]
Chronic pain	burns [14], cancer [12]
Infectious disease	HIV [39], tuberculosis [39]

[4]. Anxiety and related disorders are prevalent throughout life [19–22]. Furthermore, while the prevalence of comorbid anxiety and related disorders in those with chronic medical illness is not as well studied as depression in medical conditions, studies which have been done indicate it is as common [22–25]. A large cross-sectional study demonstrated that generalized anxiety disorder was the most prevalent anxiety disorder in primary care settings [3].

Systematic reviews have established that anxiety disorders are particularly prevalent in gastrointestinal disorders, pulmonary disease, cardiovascular disease, endocrine disease and cancer, as well as neuropsychiatric disorders such as chronic pain and migraines. In irritable bowel syndrome, up to 95% of patients have generalized anxiety disorder or panic disorder [26]. Similarly, panic disorder and generalized anxiety disorder were more prevalent in those with peptic ulcer disease [27]. In asthma, anxiety disorders occur in at least 25% of patients [28, 29]. In multiple studies of adolescents and adults with asthma, the prevalence of panic disorder and agoraphobia is almost three times that of the general population [30, 31]. Another anxiety disorder that co-occurs with respiratory illness is generalized anxiety disorder [31]. Table 1 outlines medical conditions associated with anxiety symptoms and disorders.

The co-occurrence of anxiety and general medical conditions is associated with significant impairment, morbidity and economic costs [36, 40–42]. For example, in a study of almost 500 medically ill persons diagnosed with anxiety disorders, those with posttraumatic stress disorder, panic disorder and social anxiety disorder were found more likely to be frequent consumers of healthcare, and to remain unable to maintain their roles and responsibilities, including work [43]. Medical comorbidities with anxiety disorders have also been shown to elevate suicide risk [44]. Adequate management of anxiety symptoms can improve outcomes of physical ill-health, and reduce the use of healthcare resources [4, 45]. In addition, some work suggests that quality of life and functional ability may be improved with optimal treatment of comorbid general medical and anxiety disorders [46–48].

Etiology

There is a growing body of evidence for a strong bidirectional association between anxiety and related disorders and co-occurring general medical

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conditions [14, 29, 49]. On the one hand, medical disorders may lead to fears about diagnosis, hospitalization, painful procedures and a foreshortened lifespan, while certain medical disorders may be linked physiologically to the development of anxiety and related disorders [50]. On the other hand, anxiety and related disorders may lead to vulnerability for various medical conditions. There may also be underlying factors that contribute to susceptibility for both anxiety disorders and physical conditions [51].

There is ongoing work to determine the precise nature of the relationships between anxiety disorders and physical illness in a number of areas. Thus, in irritable bowel syndrome, it has been suggested that infection or inflammation of the gastrointestinal tract lead to anxiety [29], while in asthma it has been postulated that increased partial pressure of carbon dioxide is responsible for panic attacks [52]. On the other hand, neurotransmitter disturbances and hypothalamic-pituitary-adrenal axis dysfunction have been postulated to play a key role in explaining how anxiety symptoms and disorders lead to medical illnesses [53].

The common underlying factors that may contribute to both anxiety disorders and comorbid physical illness have also received ongoing study. Genetic factors may, for example, predispose to both general medical conditions and anxiety disorders [54, 55]. In the World Mental Health Surveys, there were strong relationships between early adversity and subsequent onset of both anxiety disorders and various physical disorders, including chronic spinal pain, chronic headache, heart disease, asthma, diabetes and hypertension [56, 57].

Clinical Features

Recognition of anxiety disorders in people with medical illness can be challenging for several reasons. Firstly, anxiety symptoms are an understandable response to the diagnosis of medical conditions. A medical condition can be sufficient enough to be a stressor for an individual to develop an adjustment disorder, and in some cases even posttraumatic stress disorder. Secondly, anxiety symptoms may overlap with symptoms of an underlying medical disorder; thus, since patients with cancer may have insomnia and fatigue, conditions such as generalized anxiety disorder are overlooked. Similarly, medications used in the treatment of physical disorders may lead to anxiety symptoms [20, 49, 58].

In a patient with anxiety symptoms, a range of different diagnoses can be considered. Table 2 tabulates the main features of key anxiety and related disorders. Posttraumatic stress disorder is the anxiety and related disorder that is most commonly associated with gastrointestinal, cardiac, endocrine, chronic pain, migraines and Parkinson's disease [14, 22]. Symptoms of generalized anxiety disorder arguably most closely resemble those of many general medical conditions, particularly in the older population [20]. Panic disorder may, however, mimic a number of physical illnesses. Indeed, a broad range of different anxiety and related disorders have been associated with various physical illnesses.

Management

Early identification of anxiety symptoms and disorders in individuals with chronic illness is important in determining better outcomes for individuals with both sets of disorders [60–62]. The therapeutic alliance and collaboration between medical professionals may contribute to successful management of symptoms [50]. There is, however, a paucity of robust evidence in the treatment of chronically ill patients with comorbid anxiety and related disorders [51].

Cognitive behavioral therapy has been undertaken in a number of studies of individuals with medical illness and anxiety and related disorders. A systematic review of 32 psychotherapy

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Key Issues Ment Health. Basel, Karger, 2015, vol 179, pp 81–87 (DOI: 10.1159/000365538)

Table 2. Anxiety and related disorders commonly seen in medically ill adult patients [14, 59]

Generalized anxiety disorder	characterized by a pervasive and excessive worry about everyday life events; this worry is difficult to control and is accompanied by somatic symptoms which impair the individual's functioning
Specific phobia	characterized by excessive, irrational and persistent fear of specific objects, situations or activities such as heights, flying and spiders
Social anxiety disorder	characterized by an intense and excessive fear of scrutiny and humiliation in social situations which then leads to avoidance of these situations, or development of panic attacks when the situations are endured
Panic disorder	characterized by recurrent unexpected panic attacks described as discrete events in which the individual experiences symptoms that peak within a few minutes and resolve spontaneously, coupled with anticipatory anxiety about future panic attacks
Posttraumatic disorder	a disorder in which the individual experiences a traumatic event; the disorder is then characterized by recurrent distressing re-experiencing phenomena, increased arousal, persistent avoidance of reminders and stimuli associated with the event, and negative cognitions and mood
Hypochondriasis	characterized by preoccupation with having a severe disease; the individual cannot be reassured despite medical investigations
Obsessive-compulsive disorder	characterized by recurrent intrusive distressing thoughts or images (obsessions) which are neutralized by some other thought or repetitive mental act/behavior (compulsions)
Substance/medication-induced anxiety disorder	characterized by anxiety symptoms which are directly related to the physiological effects of a substance or medication
Adjustment disorder with anxiety	characterized by a time-limited, maladaptive anxiety response to an identifiable stressor
Separation anxiety disorder	characterized by excessive, developmentally inappropriate anxiety upon separation of the child from the home or from significant attachment figures
Anxiety disorder not otherwise specified	diagnosed when the individual's symptoms are severe and distressing but do not meet diagnostic criteria for any other anxiety disorder

trials in patients with irritable bowel syndrome and anxiety disorders indicates the efficacy of cognitive behavioral therapy in reducing somatic distress [63–65]. A systematic review of 20 studies of cognitive-behavioral interventions in nearly 3,000 participants found that they may be effective in the management of HIV-/AIDS-associated anxiety [66]. Cognitive behavioral therapy has also been shown to reduce anxiety symptoms and distress in patients with cardiac disease and anxiety in one randomized controlled trial [67].

Behavioral strategies in anxiety disorders and comorbid medical illnesses include biofeedback, relaxation training and meditation [68, 69]. Two randomized controlled trials examining the effects of biofeedback in the management of asthma [69], and another two randomized controlled trials looking at relaxation therapy showed a reduction in the use of bronchodilator agents and improved quality of life [70].

Hypnotherapy and interpersonal therapy are other treatment modalities showing promise in the management of pain related to procedures for

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cancer therapies [71, 72], but rigorous studies are lacking in this area [14, 64].

In patients with physical illness and anxiety and related disorders, there are relatively few randomized controlled trials to guide treatment choices. Thus, medications should be selected based on studies of efficacy in anxiety disorders, and on minimizing adverse events and drug-drug interactions. The selective serotonin reuptake inhibitors sertraline, citalopram and escitalopram have relatively few adverse events and are safe in interaction with other agents [73]. The serotonin-noradrenaline reuptake inhibitors venlafaxine and duloxetine have the potential advantage of being beneficial for pain symptoms, but venlafaxine has the disadvantage of requiring blood pressure monitoring [74]. Drugs such as mirtazapine and the tricyclic antidepressants may be efficacious in the treatment of some anxiety disorders, but carry a significant side-effect profile and may have worrisome drug-drug interactions [74]. Benzodiazepines and sedative-hypnotic agents may be helpful for anxiety symptoms, but should be used cautiously due to concerns of dependence [6]. The second-generation antipsychotic quetiapine is anxiolytic at low doses, and is efficacious in the treatment of some anxiety and related disorders [50], but its metabolic, cardiac and autonomic side-effect burden should be taken into consideration.

Conclusion

Anxiety and related disorders are frequently comorbid with chronic medical conditions. There is growing understanding of the bidirectional relationships between these sets of disorders. Recognition can be delayed due to the similarity of primary anxiety symptoms and anxiety secondary to general medical conditions. Pharmacotherapy management can be effective, but clinicians need to be aware of the side-effect burden of psychotropics in medical conditions as well as potential drug-drug interactions. There is a growing database of studies of cognitive-behavioral therapy showing efficacy in individuals with anxiety disorders and comorbid medical illness. Further work is needed to improve screening for anxiety and related disorders in medical illness, to enhance diagnosis and assessment, and to optimize treatment.

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EXHIBIT 18

brain sciences

MDPI

Review

Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications

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Abstract: Bipolar disorder (BD) is strongly associated with immune dysfunction. Replicated epidemiological studies have demonstrated that BD has high rates of inflammatory medical comorbidities, including autoimmune disorders, chronic infections, cardiovascular disease and metabolic disorders. Cytokine studies have demonstrated that BD is associated with chronic low-grade inflammation with further increases in pro-inflammatory cytokine levels during mood episodes. Several mechanisms have been identified to explain the bidirectional relationship between BD and immune dysfunction. Key mechanisms include cytokine-induced monoamine changes, increased oxidative stress, pathological microglial over-activation, hypothalamic-pituitary-adrenal (HPA) axis over-activation, alterations of the microbiome-gut-brain axis and sleep-related immune changes. The inflammatory-mood pathway presents several potential novel targets in the treatment of BD. Several proof-of-concept clinical trials have shown a positive effect of anti-inflammatory agents in the treatment of BD; however, further research is needed to determine the clinical utility of these treatments. Immune dysfunction is likely to only play a role in a *subset* of BD patients and as such, future clinical trials should also strive to identify which specific group(s) of BD patients may benefit from anti-inflammatory treatments.

Keywords: bipolar disorder; inflammation; cytokines; depression; neuroprogression; cognition; N-acetylcysteine; infliximab; celecoxib; minocycline

1. Introduction

Bipolar disorder (BD) is a severe and persistent mental illness associated with significant morbidity and mortality. While numerous hypotheses have been proposed to explain the underlying patho-etiology of BD, the mechanisms sub-serving disease onset and progression remain largely unknown. More recently, immune dysfunction has been implicated in the patho-etiology of BD [1]. The hypothesis that immune dysfunction may be a mediator of disease progression in BD was first proposed by Horrobin & Lieb (1981) [2] who hypothesized that immune modulation may be a key mechanism of action in lithium's mood stabilizing effects. They further hypothesized that the relapsing-remitting nature of BD may be driven by the immune system, as seen in other relapsing-remitting inflammatory disorders, such as multiple sclerosis (MS) [2]. Since their hypothesis was proposed, numerous investigators have studied the interaction between BD and immune dysfunction [1,3–5].

The primary aim of the current review is to summarize and synthesize studies assessing the interaction between BD and immune dysfunction. Towards this end, we will summarize the following key areas: (1) epidemiological data revealing high rates of comorbidity between BD and inflammatory disorders; (2) cytokine studies showing increased central and peripheral levels of pro-inflammatory

molecules in BD compared to healthy controls; (3) proposed pathophysiological mechanisms sub-serving the inflammatory-mood pathway and (4) clinical implications of the interaction between BD and immune dysfunction, with a focus on repurposing anti-inflammatory agents in the treatment of bipolar depression.

Of note, the current review is not a systematic review, but rather narrative in nature, to provide a broad overview of the topic. A systematic review was not conducted given the breadth of the topic and vast number of studies on the various elements of the interactions between BD and inflammation. As such, the authors decided to focus on particularly relevant studies rather than exhaustively reviewing all published articles. The authors acknowledge that this approach is vulnerable to the presentation of a biased perspective; however, have attempted to present in an unbiased manner, highlighting areas of controversy and disagreement when needed.

2. Bipolar Disorder and Inflammatory Comorbidities

One potential indicator to suggest an interaction between BD and immune dysfunction is the high rates of inflammatory medical comorbidities in BD [6]. The association between BD and inflammatory comorbidities has been well established in numerous epidemiological studies; however, the direction of causality remains somewhat unclear. As shown in Figure 1a, immune dysfunction may be a common underlying cause of both BD and an inflammatory comorbidity in a given patient. Alternatively, BD may proceed the inflammatory condition or vice versa (Figure 1b,c). All three scenarios are observed in the BD population suggesting that the interaction is likely bidirectional in that immune dysfunction, BD and inflammatory comorbidities may be perpetuating each other as shown in Figure 1d [6]. Further, genetic and environmental risk factors for immune dysfunction may simultaneously increase the risk of developing both BD and other inflammatory comorbidities. Herein we summarize pertinent epidemiological findings showing the association between BD and inflammatory comorbidities.

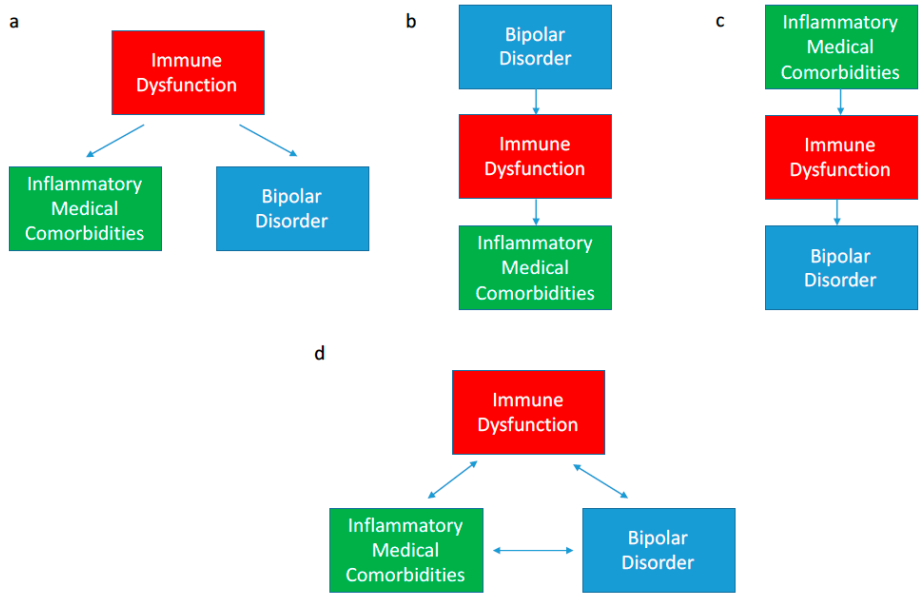

Figure 1. Potential interactions between bipolar disorder (BD), immune dysfunction and inflammatory comorbidities. (**a**) Immune dysfunction may be a common underlying cause of both BD and an inflammatory comorbidity; (**b**) BD may proceed the inflammatory condition or (**c**) vice versa. All three scenarios are observed in the BD population suggesting that the interaction is likely bidirectional in that immune dysfunction, BD and inflammatory comorbidities may be perpetuating each other (**d**).

When an inflammatory comorbidity is present, peripherally released pro-inflammatory cytokines may increase systemic cytokine levels (e.g., IL-2, IL-6, TNF-α) throughout the body, including in

the brain [7]. The subtler effects of chronic low grade systemic inflammation on off-target areas (e.g., the brain) has been increasingly recognized as important [8,9]. Admittedly, the association between BD and inflammatory comorbidities does not, in itself, prove causation, however, the biological mechanisms [10] to be further discussed in Section 4 provide further evidence that these epidemiological observations (summarized in Table 1) are likely to be more than just spurious associations.

Table 1. Inflammatory comorbidities associated with bipolar disorder, as shown by epidemiological studies.

Category	Specific Conditions
Autoimmune disorders	Inflammatory bowel disease (IBD) Systemic lupus erythematosus (SLE) Autoimmune thyroiditis Guillain-Barré syndrome (GBS) Autoimmune hepatitis Rheumatoid arthritis (RA) Multiple sclerosis (MS) Psoriasis
Chronic infections	Toxoplasma gondii (*T. gondii*), Possibly herpes simplex virus 1 (HSV1), cytomegalovirus (CMV) and human herpes virus 6 (HHV6)
Cardiovascular disease	Myocardial infarction Stroke Atherosclerosis Hypertension
Metabolic disorders	Type II diabetes mellitus
	Dyslipidemia
	Central obesity
	Metabolic syndrome
	Gout

2.1. Bipolar Disorder and Autoimmune Disorders

Autoimmune disorders represent the most "classic" of inflammatory conditions in that they are defined by the presence of immune dysfunction. In brief, autoimmune disorders occur when the immune system misrecognizes host tissue as pathogenic and attempts to remove the misidentified host tissue [11]. In doing so, both a local and systemic inflammatory response is initiated. Locally, the immune system attempts to break down and clear the triggering tissue (e.g., local break down of skin in psoriasis). While triggering this local inflammatory response, pro-inflammatory cytokines are released and circulated systemically with some degree of penetration to the central nervous system (CNS) as well. As a group, autoimmune disorders have been identified to occur at increased rates in BD [6]. Epidemiological studies have consistently shown increased rates of inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), autoimmune thyroiditis, psoriasis, Guillain-Barré syndrome (GBS), autoimmune hepatitis, MS and rheumatoid arthritis (RA) in BD [12–18].

2.2. Bipolar Disorder and Chronic Infections

Infections are also classically associated with both a local and systemic inflammatory response. The inflammatory response to infections is an essential physiological response that has been evolutionarily conserved amongst all mammal species [11]; however, in the case of chronic infections, the prolonged inflammatory response may also have deleterious effects, as the immune response is best suited for clearing an acute infection [19]. Similar to autoimmune disorders, chronic infections

may lead to chronic elevation of pro-inflammatory cytokines systemically and centrally. As such, an association between chronic infections and BD may be expected.

Dating back to the 19th century, there has been significant interest in the interaction between BD and chronic infections, such as Toxoplasma gondii (*T. gondii*), herpes simplex viru 1 (HSV1), cytomegalovirus (CMV) and human herpes virus 6 (HHV6); however, results have been mixed with poor replicability of identified associations [20]. The strongest replicated evidence has shown an increased co-prevalence of *T. gondii* in BD compared to the general population (odds ratio (OR) 1.52, $p = 0.02$) [21]. Interestingly, chronic infections, such as *T. gondii*, CMV and HSV1 have been associated with poorer cognitive function in BD [22,23]. Taken together, the association between BD and chronic infections remains unclear; however, BD patients with comorbid chronic infections may be at risk for a more severe phenotype secondarily to the presence of chronic low grade inflammation.

2.3. Bipolar Disorder and Cardiovascular Disease

Immune dysfunction is a key feature of cardiovascular disease (CVD) as inflammation plays a significant role in the progression of atherosclerotic plaques [24]. Cardiovascular disease has been strongly associated with BD in a bidirectional fashion. To emphasize the importance of this association, the American Heart Association (AHA) has recently recognized BD as an independent risk factor of early CVD. Indeed, replicated epidemiological studies have identified BD as an independent risk factor for CVD and vice versa [25–30]. Both cardiovascular and psychiatric researches have pointed to immune dysfunction as a likely key factor mediating this observed interaction. The high rate of comorbid BD and CVD is of particular importance because of its role in early mortality in BD; the increased prevalence of CVD is primarily responsible for the 10- to 20-year decrease in life expectancy in BD compared to the general population [31]. With this interaction in mind, some investigators have suggested that targeting immune dysfunction in this patient population may serve to simultaneously improve outcomes for BD, CVD and overall life expectancy [1,28].

2.4. Bipolar Disorder and Metabolic Disorders

Similar to CVD, immune dysfunction plays a key role in the progression of metabolic disorders [26,32,33]. Diabetes and central obesity have both been associated with chronic low grade inflammation, with the degree of inflammation being directly correlated with disease progression [34]. With immune dysfunction as a likely key mediating factor, BD has been strongly associated with increased rates of diabetes, obesity, dyslipidemia and metabolic syndrome [12,35,36].

A key factor facilitating chronic inflammation related to metabolic disorders is the presence of visceral adipose tissue (i.e., central obesity). Visceral adipose tissue is a direct source of chronic low-grade inflammation, increasing the production of pro-inflammatory adipokines and cytokines including IL-6, TNF-α, and C-reactive protein (CRP) [37,38]. Subcutaneous adipose tissue serves as a "metabolic sink" to prevent accumulation of visceral adipose tissue; however, under certain genetic (e.g., polygenic risk factors for central obesity) and environmental (e.g., sedentary lifestyle and poor diet) conditions, high volumes of dysfunctional visceral adipose tissue may accumulate [37,38]. In the context of chronic positive energy balance (e.g., greater caloric intake then expenditure), adipocytes undergo hypertrophy and have increased triglyceride stores [39]. The lypolytic rate is therefore increased leading to increased production of leptin (pro-inflammatory) and decreased production of adiponectin (anti-inflammatory), thereby signaling the release of pro-inflammatory cytokines [40]. Further, adipocyte hypertrophy promotes macrophage infiltration of adipose tissue. The resultant cross talk between macrophages and adipocytes promotes further release of pro-inflammatory cytokines and adipokines [37–40].

Bipolar disorder has also been associated with a slightly increased risk of developing gout [41]. With this epidemiological observation in mind, several investigators have recently hypothesized that purinergic system abnormalities and related variations of uric acid may be involved in the pathophysiology of BD [42,43]. Uric acid has been strongly associated with other metabolic disorders,

increased oxidative stress and inflammation [44,45]. Further, several proof-of-concept clinical trials have identified a potential anti-manic effect of drugs lowering uric acid (e.g., allopurinol) [46].

3. Cytokine Changes Associated with Bipolar Disorder

Cytokines are signaling molecules of the immune system which may increase or decrease local and systemic inflammatory responses. Measuring cytokine levels peripherally (i.e., serum levels) and centrally (i.e., cerebral spinal fluid (CSF) levels) provides insight into immune system activity. Cytokine levels can identify current levels of inflammation and identify which specific part of the immune system is over or underactive leading to the observed immune dysfunction in BD. Moreover, as signaling molecules, specific cytokines may be directly implicated in the pathophysiology of BD and may therefore present as potential novel targets of treatment.

Cytokine levels have significant fluctuations and variability; however, some trends have emerged through numerous cytokine studies of BD patients compared to healthy controls [3,4]. These cytokine studies have consistently shown elevated levels of pro-inflammatory cytokines in BD, suggestive of chronic low grade inflammation. Serum levels of pro-inflammatory molecules including interleukin-4 (IL-4), tumor necrosis factor alpha (TNF-α), soluble interleukin-2 receptor (sIL-2R), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), soluble receptor of TNF-α type 1 (STNFR1) and CRP are elevated in BD patients compared to healthy controls [3,47–49]. This cytokine profile indicates dysfunction of the *innate* immune system.

Another key observation has been variability in cytokine profiles depending on mood state (i.e., differing cytokine profiles during periods of depression, mania, hypomania and euthymia). This variability in cytokine profiles might suggest variable involvement of immune dysfunction in depression versus mania versus euthymia. Significant heterogeneity in BD cytokine studies has been problematic and, as such, there has been no clear cytokine profile that is reproducibly associated with each mood state [3,4]. This significant heterogeneity also suggests that inflammation is likely a pertinent pathogenic factor for only a *subset* of BD; this subset of BD may potentially represent an "inflammatory-BD" that may be pathophysiologically dissimilar from other BD patients. This potential sub-typing of BD is currently being investigated with important treatment implications.

Within the context of this substantial heterogeneity, the following mood-dependent cytokine profiles have been identified. The most robust evidence exists for an association between pro-inflammatory cytokines and depressive episodes, in both bipolar and unipolar depression [50]. During depressive episodes, serum levels of CRP, TNF-α, IL-6, IL-1β, sTNFR1 and CXCL10 are elevated [10,47,51]. Increased depression severity is associated with greater elevations of pro-inflammatory cytokines [52]. During manic episodes, serum levels of IL-6, TNF-α, sTNFR1, IL-RA, CXCL10, CXCL11 and IL-4 are often elevated [47,51]. During euthymic periods, sTNFR1 is the only consistently elevated inflammatory marker [47,48]. One significant limitation of these cytokine studies is their cross-sectional nature (i.e., serum levels are usually only taken at one point in time). Longitudinal studies are needed to measure cytokine levels within the same group of BD subjects to determine how they change during and in between mood episodes. Understanding this chronological relationship (e.g., if cytokines are elevated prior to versus after mood episode onset) would also provide further insight into the cross-talk between BD and immune dysfunction.

4. Pathophysiology of the Inflammatory-Mood Pathway

Numerous mechanisms have been identified which may mediate the bidirectional interaction between BD and immune dysfunction. Many of these mechanisms have been largely established in animal models [53]. More recently, clinical studies have provided evidence to suggest that these preclinical findings are valid in humans as well [10,54]. Herein we describe some of the key biological mechanisms which may contribute to the inflammatory-mood pathway. Of note, many of these mechanisms are not exclusive to BD and may trans-diagnostically sub-serve the interactions observed between immune dysfunction and other brain disorders (e.g., unipolar depression, schizophrenia,

neurodegenerative disorders) [55]. Currently, it remains unclear the degree of overlap versus divergence in inflammatory processes mediating the interaction between immune dysfunction and various neuropsychiatric disorders [56]. We hypothesize that there are likely both trans-diagnostically shared immune pathways as well BD-specific immune pathways (i.e., immune changes and mechanism that may not be present in other disorders).

Central to the inflammatory-mood pathway is the ability of peripherally circulating cytokines to traverse the blood-brain-barrier (BBB). Systemically circulating cytokines may traverse the BBB via active transport channels and through leaky regions of the BBB [57]. Of note, the relative permeability of the BBB for various cytokines remains unclear; however, replicated evidence has demonstrated clear associations between elevation of cytokines in serum samples (i.e., peripherally circulating cytokines) with the same cytokines being elevated in cerebral spinal fluid (CSF) samples (i.e., cytokine levels in the CNS), suggesting that likely all cytokines may penetrate the CNS to some degree [47]. Recent findings in animal models have also suggested the presence of lymphatic vessels in the brain which could provide another direct pathway for cytokines and other signalling molecules to enter the CNS [58]. Cytokines may then signal several downstream effects which alter the structure and function of key brain regions sub-serving mood and cognitive function. Cytokines can directly alter monoamine levels, cause over-activation of microglial cells and lead to increased oxidative stress in the brain [53]. The net effect of these changes is neurodegeneration and decreased neuroplasticity in key brain regions which may lead to the phenotypic changes observed in BD and other brain disorders.

4.1. Cytokine-Induced Neurotransmitter Changes

Monoamine changes have been the focus of mood disorder research for many years. Further, the majority of psychiatric medications' primary mechanism of action is through alteration of monoamine levels [59]. Pro-inflammatory cytokines may directly and indirectly alter monoamine levels in the CNS through numerous pathways. More specifically, TNF-α, IL-2 and IL-6 have been shown to directly alter monoamine levels [60]. IL-2 and interferon-gamma and alpha (IFN-γ and -α) increase the enzymatic activity of indolamine 2,3-dioxygenase (IDO), thereby increasing the breakdown of tryptophan to depressogenic tryptophan catabolites (TRYCATs). Serotonin (5-HT) levels may be further modulated through the IL-6 and TNF-α dependent breakdown of 5-HT to 5-hydroxyindoleacetic acid (5-HIAA) [61]. Depletion of tryptophan and decreased levels of 5-HT can directly impair affective and cognitive function [62].

Inflammation may also directly alter levels of dopamine and norepinephrine. Pro-inflammatory molecules, such as IFN, induce the activation of the guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) enzyme. Increased expression of GTP-CH1 results in the formation of neopterin and tetrahydrobiopterin (BH4), a cofactor used by phenylalanine hydroxylase (PH), tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH) to form tyrosine (Tyr), dopamine, norephinephrine, and serotonin, respectively; however, inflammation lowers pyruvoyl tetrahydropterin synthase (PTPS) activity, thus favouring neopterin formation instead of BH4 [63–65]. With decreased BH4 levels, the activity of PH, TH and TPH is decreased thus lowering the production of dopamine, norepinephrine and serotonin [55,66,67].

Taken together, pro-inflammatory signaling may decrease the levels of dopamine, norepinephrine and serotonin, which has long been associated with worsening mood and cognitive symptoms. Current pharmacotherapies target the end result of this pathway, namely, monoamine levels [59]. Targeting inflammation may have more disease modifying potential as immune dysfunction is "upstream" of the monoamine changes observed in mood disorders; correcting the underlying cause (i.e., immune dysfunction) may provide greater benefits than only treating symptomatically by correcting the downstream effect (i.e., monoamine changes).

Of recent interest has also been the potential interaction between inflammation and another key neurotransmitter, namely, glutamate. The importance of the glutamate system in mood disorder pathophysiology has been highlighted by the robust evidence demonstrating the rapid and

potent antidepressant effects of ketamine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist [68,69]. Significant cross-talk between glutamate and the immune system has now been demonstrated in pre-clinical and clinical models [70]. Inflammatory cytokines have been shown to influence glutamate metabolism through direct effects on microglia and astrocytes. As such, inflammatory cytokines may increase glutamate levels thus causing abnormal over-activation of glutamate receptors leading to uncontrolled increases of calcium influx through NMDA receptor channels, with the final result of excitotoxicity and impaired neuroplasticity [71].

The administration of exogenous pro-inflammatory cytokines has been shown to increase glutamate levels in the basal ganglia and anterior cingulate cortex (key brain regions sub-serving mood disorder pathology) as measured by magnetic resonance spectroscopy (MRS) [72]. Further, MRS studies in patients with unipolar depression have revealed that increased markers of inflammation (e.g., CRP) correlate with increased glutamate levels in the basal ganglia, which was specifically associated with anhedonia and psychomotor retardation [73]. In addition, an antidepressant response to ketamine may be predicted by elevated baseline inflammatory markers [74,75], further suggestive of significant cross-talk between immune dysfunction, the glutamate system and mood disorder pathophysiology.

4.2. Pathological Microglial Over-Activation

Microglia are the macrophages of the CNS that serve an important role in facilitating neuroplasticity [76–78]. Microglia aid in the pruning of unused neural circuits to allow for more space and energy to be made available for more frequently used neural circuits. Under physiological conditions, microglia may effectively prioritize the most important neural circuits leading to optimal brain structure and function [77,78]. However, with chronic inflammation, pro-inflammatory cytokines promote prolonged over-activation of microglia [76]. With this over-activation, microglia may aberrantly prune important neural circuits sub-serving mood and cognitive function (e.g., prefrontal cortex (PFC), amygdala, hippocampus, insula and the anterior cingulate cortex (ACC)) [76,79]. This process results in a positive feed-forward loop whereby activated microglia release cytokines, which further increases inflammation and further microglia recruitment and activation. The release of cytokines from activated microglia may also further perpetuate the previously discussed monoamine changes. Lastly, the over-activation of microglia increases the production of reactive oxygen species (ROS) leading to local oxidative stress, further damaging neural circuitry in key brain regions sub-serving mood and cognition [80]. This unfortunate cascade may contribute to the neuroprogression of BD as increasing numbers of important neural circuits are destroyed [47,81–83].

4.3. Inflammation and Increased Oxidative Stress

Oxidative stress has also been associated with mood disorders and is intimately connected with immune dysregulation, as inflammation increases oxidative stress and oxidative stress increases inflammation [84–86]. Oxidative stress occurs when there is an imbalance between the production of ROS and production of antioxidants responsible for neutralizing ROS [87]. Replicated evidence has demonstrated increased ROS and decreased antioxidants in BD, leading to pathologic neurodegeneration in key brain regions sub-serving mood and cognition [88–90]. Mood disorders have been associated with increased levels of pro-oxidant markers, namely, 8-hydroxy-2′-deoxyguanosine (8-OHdG), F2-isoprostanes, malondialdehyde (MDA) and decreased levels of anti-oxidant molecules, namely, glutathione (gamma-glutamyl-cysteinyl-glycine; GSH), superoxide dismutase (SOD) and glutathione peroxidase (GPx) [91]. Further, in unipolar depression, antidepressant response (to conventional antidepressants) has been associated with decreased oxidative stress, suggesting a mediational role of oxidative stress reduction in the effective treatment of mood disorders [87]. As such, there has been great interest in further understanding the mechanisms sub-serving increased oxidative stress along with the potential novel drug targets these mechanisms may offer.

4.4. Hypothalamic-Pituitary-Adrenal (HPA) Axis Over-Activation

Pro-inflammatory cytokines, namely IFN, TNF-α and IL-6, significantly up-regulate HPA activity thereby increasing systemic cortisol levels [92]. Under physiological conditions, HPA activation is advantageous to aid in the stress response required with an acute infection or injury. However, with chronic inflammation, HPA activation may be prolonged with deleterious effects related to chronic hypercortisolemia [93]. Additionally, chronic hypercortisolemia leads to downregulation of glucocorticoid receptor synthesis, translocation and sensitivity in the pituitary and hypothalamus, effectively inhibiting the negative feedback loop of the HPA axis [94]. This loss of the negative feedback loop leads to further propagation of hypercortisolemia with the well-established negative downstream effects (e.g., mood, cognitive and physical squealy) of chronically elevated cortisol levels [95–98]. Further, impaired cortisol suppression itself has long been recognized a strong predictor of mood disorders [98].

Dysfunction of the HPA axis has been identified in numerous medical and psychiatric disorders, however, the particular relevance in BD, in specific, was further emphasized by a recent meta-analysis and systematic review [99]. Belvederi Murri et al., (2016) identified forty-one studies showing that BD was consistently associated with significantly increased levels of cortisol (basal and post-dexamethasone) and adrenocorticotropic hormone (ACTH), but not of corticotropin-releasing hormone (CRH). These authors suggested that progressive HPA axis dysfunction is a putative mechanism that might underlie the clinical and cognitive deterioration of patients with BD and that targeting the HPA axis might be a novel strategy to improve the outcomes of BD [99].

4.5. The Microbiota-Gut-Brain Axis

In recent years, the role of the microbiota-gut-brain axis in neuropsychiatric disorders has become of great interest [100–102]. The gut and brain may communicate in a bidirectional fashion through numerous pathways including via the parasympathetic nervous system (primarily the vagus nerve), the gut neuroendocrine system, the circulatory system (delivering neuroactive metabolites and neuro-transmitters directly produced in the gut), and most notably, via the immune system [101]. The composition of the gut microbiota may have a large impact on the signaling molecules, including cytokines, that are being produced by the gastrointestinal (GI) system. The GI system may induce the production of pro-inflammatory cytokines on an acute or chronic basis. These cytokines may have direct effects on brain function as previously described.

Numerous investigators are questioning the potential impact of altering the gut microbiota on immune function and mental illness [103]. While this field is still in its infancy, the potential for novel treatments targeting the gut microbiota to treat BD may represent a completely new class of hypothesis-driven therapeutic interventions. For example, in a recent case report, Hamdani et al., (2015) suspected that a manic episode may have been triggered by alteration of the gut microbiota [104]. Given their hypothesis that the manic episode was triggered by perturbation of the gut-brain axis, the patient was treated with daily activated charcoal (a potent absorbent of gut inflammatory cytokines) instead of conventional anti-manic agents. The manic episode was successfully treated which corresponded to decreased serum levels of pro-inflammatory cytokines and chemokines. While targeting the microbiota to treat BD has yet to be assessed in any clinical trials, this case reports shows promise for a potential role of this novel target.

4.6. Inflammation and Sleep Dysfunction

Sleep dysfunction is a key feature of BD. During all phases of illness, changes in sleep patterns are commonly reported [105]. Indeed, during manic or hypomanic episodes, there is a characteristic decreased need for sleep. During depressive episodes, there may be difficulties achieving adequate quality or quantity of sleep or alternatively, hypersomnia in which patients are sleeping many more hours than would be typical for the general population. Even during euthymic periods, sleep

complaints are still common in BD [105]. Sleep dysfunction is also strongly associated with immune dysfunction. Replicated evidence has demonstrated sleep dysfunction to be associated with increased levels of pro-inflammatory cytokines with a bidirectional causal association identified [106,107]. As such, interest has grown in immune dysfunction as a potential nexus sub-serving the bidirectional interaction between sleep dysfunction and BD [108,109].

5. Clinical Implications

Currently available treatments for BD have poor long term outcomes with high rates of treatment resistance and relapse [110]. Additionally, tolerability is often poor with significant adverse effects, such as weight gain and insulin resistance, being common with most evidence-based treatments [111]. Given the significant interaction between immune dysfunction and BD, the immune system presents as a potential novel target in the treatment of BD. The evidence discussed above suggests that inflammation may play a direct effect in the pathophysiology of BD in a subset of patients. Therefore, repurposing anti-inflammatory agents in the treatment of BD may potentially have disease modifying effects by targeting the underlying etiological processes rather than only treating symptomatically (i.e., the current approach).

Several proof-of-concept clinical trials have assessed the antidepressant effects of anti-inflammatory agents in the treatment of both unipolar [112] and bipolar [113] depression. In a recent meta-analysis conducted by our group to evaluate the antidepressant effects of anti-inflammatory agents, we identified eight randomized clinical trials (RCTs) (n = 312) assessing adjunctive nonsteroidal anti-inflammatory drugs (n = 53), omega-3 polyunsaturated fatty acids (n = 140), N-acetylcysteine, (n = 76), and pioglitazone (n = 44) in the treatment of BD. The overall effect size of adjunctive anti-inflammatory agents on depressive symptom severity was −0.40 (95% confidence interval −0.14 to −0.65, p = 0.002), indicative of a moderate antidepressant effect with good overall tolerability [113]. The clinical applicability of this meta-analysis was limited by the small number of studies included and small pooled sample size; however, this analysis provided further proof of concept that targeting the immune system may be an efficacious novel treatment for BD. Herein we further summarize clinical trials assessing specific anti-inflammatory agents in the treatment of BD.

5.1. N-Acetyl-Cysteine (NAC)

Among all anti-inflammatory agents, NAC has the strongest evidence as an adjunctive treatment for bipolar depression [114,115]. In an RCT of NAC for BD (n = 75), adjunctive NAC was shown to lower depression severity scores throughout the trial with a statistically and clinically significant difference compared to conventional therapy alone at the primary endpoint of 24 weeks [114]. Additionally, post-hoc analysis of 17 participants from this sample who met criteria for a current major depressive episode (MDE) at baseline revealed that 8 of 10 participants in the NAC group had a clinical response (i.e., greater than 50% reduction in depression severity) compared to only 1 of 7 participant in the placebo group [116]. An eight-week open-label trial of NAC also showed antidepressant effects in BD [117]. The effect of adjunctive NAC in mania/hypomania was also explored in a small post-hoc analysis of 15 BD participants experiencing an acute manic/hypomanic episode comparing participants receiving adjunctive NAC (n = 8) versus adjunctive placebo (n = 7). This analysis revealed a greater improvement in symptoms of mania in the NAC group compared to placebo [118]. Overall, NAC shows promise as an adjunctive treatment for BD during all phases of illness; however, evidence is strongest for use in the acute treatment of bipolar depression.

5.2. Omega-3 Polyunsaturated Fatty Acids (Omega-3s)

Several RCTs have also evaluated the effects of adjunctive omega-3s, a naturally-occurring and well-tolerated anti-inflammatory agent [119]. Results have been mixed with some trials showing an antidepressant effect in BD [120,121] and others reporting no antidepressant effect compared to

conventional therapy alone [122–124]. When pooling these results together in a recent meta-analysis, a moderate and statistically significant anti-depressant effect of adjunctive omega-3s in BD was found compared to conventional therapy alone [119].

The mixed results of these studies assessing omega-3s in BD may suggest that omega-3s are beneficial in only a subset of BD. This hypothesis was further supported by a recent study assessing the antidepressant effects of omega-3s in the treatment of unipolar depression [125]. In this RCT, omega-3s were found to have a significant antidepressant effect in participants with elevated inflammatory markers. Intriguingly, in participants with normal cytokine levels, placebo had a greater antidepressant effect, compared to omega-3s, leading to an overall negative study outcome (i.e., no significant antidepressant effect was found when including the entire sample). While this study was in unipolar depression, it is likely that a similar effect may be observed in BD, in that only patients with elevated inflammatory markers may benefit from omega-3s, however, further study is still required to confirm or refute this hypothesis in the BD population.

5.3. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The anti-depressant effect of adjunctive NSAIDs has also been evaluated in BD. Nery et al., assessed adjunctive celecoxib in BD (n = 28) during an acute depressive or mixed episode [126]. Adjunctive celecoxib lowered depression severity by week 1; however, the primary outcome was negative as change in depression severity converged with the placebo group by the end of week 6. Saroukhani et al., assessed the effect of adjunctive aspirin in an RCT with male BD patients (n = 32) and found no significant difference between treatment groups by the primary endpoint of 6-weeks [127].

Three studies have also evaluated the effect of NSAIDs during acute manic/hypomanic episodes. In a small, proof-of-concept RCT, Arabzadeh et al., compared adjunctive celecoxib to treatment as usual for acute mania in BD inpatients (n = 46) [128]. They observed a significantly higher remission rate in the celecoxib group (87.0%) compared to the placebo group (43.5%) by the week 6 primary endpoint (p = 0.005). The same investigators also evaluated adjunctive celecoxib in an RCT of adolescent inpatients (n = 42) during an acute manic episode [129]. There was no significant difference in remission rates by the primary endpoint of 8-weeks, however, significantly greater improvement was observed in Young Mania Rating Scale (YMRS) scores in the celecoxib group compared with the placebo group by the week 8 primary endpoint (p = 0.04). In another RCT including BD inpatients (n = 35) with mania receiving electroconvulsive therapy (ECT), participants received either celecoxib or placebo from one day before the first ECT session throughout the sixth session. Brain-derived neurotrophic factor (BDNF) levels were also measured before and during the trial. Adding celecoxib was not associated with a significant rise in BDNF levels following ECT. No difference was noted between groups in terms of treatment response [130].

Taken together, the effect of NSAIDs in bipolar depression remains unclear as clinical studies have yielded mixed results. Additionally, adjunctive NSAIDs in the treatment of mania has yielded mixed results with anti-manic effects yet to be consistently demonstrated.

5.4. Minocycline

Minocycline is a tetracycline antibiotic with potent anti-inflammatory and neuroprotective effects [131]. Since the first case report of minocycline for bipolar depression was published in 1996 [132], there has been significant interest and off-label prescribing of minocycline for bipolar and unipolar depression; however, until this year (2017) there were no published RCTs to support or refute the antidepressant effects of minocycline. Recently, several open label trials and RCTs have been conducted to evaluate the antidepressant effects of minocycline for bipolar and unipolar depression [133–137]. In a recently published pilot, open-label, 8-week study, Soczynska et al., (2017) evaluated the efficacy, safety and tolerability of adjunctive minocycline for the treatment of bipolar I/II depression [134]. Adjunctive minocycline was associated with a significant reduction in depressive symptom severity from baseline to week 8 with overall good tolerability. While there has yet to be an

RCT of minocycline for bipolar depression, these results show promise for a significant antidepressant effect and merit further investigation.

5.5. TNF-α Inhibitors

TNF-α inhibitors have also been of interest as they may directly target a key cytokine (i.e., TNF-α) known to be implicated in the inflammatory-mood pathway. One pivotal RCT assessed infliximab in treatment resistant depression (n = 60), including both bipolar and unipolar depressed patients in their sample. Although the overall antidepressant effect was negative for this study, a significant antidepressant effect was observed for a subgroup of participants, namely, those with elevated levels of serum CRP and TNF-α [138]. Similar to the previously discussed omega-3 RCT [125], the results of this trial suggested that stratification using inflammatory biomarkers might help determine which patients may benefit from anti-inflammatory treatments. A 12-week RCT evaluating the effects of adjunctive infliximab for the treatment of BD patients with elevated inflammatory markers is currently underway, directly implementing this type of stratified approach (NCT02363738).

5.6. Anti-Inflammatory Effects of Conventional Mood Stabilizers

Also of interest has been understanding the relative impact of conventional mood stabilizers on the immune system. Indeed, as previously discussed, the initial hypothesis of conceptualizing BD as an immune disorder was developed through observing the immune-modulating effects of lithium, one of the oldest and most effective treatments of BD [2]. The interaction between lithium and the immune system is complex as lithium has been shown to have both anti-inflammatory (e.g., suppression of cyclooxygenase-2 expression, inhibition of IL-1β and TNF-α production, and enhancement of IL-2 and IL-10 synthesis) and pro-inflammatory effects (e.g., induction of IL-4, IL-6 and other pro-inflammatory cytokines synthesis) [139,140]. As such, the 'net effect' of lithium on immune function may vary greatly; however, long term lithium use has been associated with normalization of cytokine levels [141].

Compared to lithium, much less in know about the impact of valproic acid on the immune system. Pre-clinical studies have suggested possible anti-inflammatory effects of valproic acid, however, clinical studies have failed to demonstrate a significant anti-inflammatory effect, as determined by changes in cytokine levels pre- and post-treatment [142,143]. The impact of carbamazepine, lamotrigine and antipsychotics on the immune system also remains unclear due to a lack of clinical studies [141].

6. Conclusions

Bipolar disorder is strongly associated with immune dysfunction. Moreover, in a subset of BD, immune dysfunction is likely playing a key role in the pathophysiology of disease progression. The bidirectional interaction of BD with immune dysfunction is likely responsible for the high rates of inflammatory comorbidities, such as autoimmune disorders, cardiovascular disease and metabolic disturbances. This interaction is of particular importance as medical comorbidity is primarily responsible for early mortality in BD. Numerous biological mechanisms of the inflammatory-mood pathway have been identified that may present novel targets in the treatment of BD. Targeting the immune system shows promise for improving BD outcomes as it may allow for disease modification through treatment of the underlying etiology (i.e., immune dysfunction), rather than only superficially treating the downstream effects as symptoms arise. Numerous proof-of-concept clinical trials have demonstrated a positive effect of anti-inflammatory agents in BD with generally good tolerability. Currently available evidence suggests that anti-inflammatory agents may be specifically helpful in the treatment of bipolar depression. Conversely, the impact of anti-inflammatory agents in mania and hypomania remains unclear. Clinical studies have also suggested that anti-inflammatory agents may be only beneficial for a subset of BD patients, namely, patients with immune dysfunction, as indicated by elevation of inflammatory markers. As such, future clinical trials should stratify patients based on inflammatory profile to determine which specific anti-inflammatory agent(s) are efficacious in which specific subset of BD patients.

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EXHIBIT 19

ELSEVIER

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Depression and immune function
Central pathways to morbidity and mortality

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Abstract

Objective: The increased morbidity and mortality associated with depression is substantial. In this paper, we review evidence suggesting that depression contributes to disease and death through immune dysregulation. **Method:** This review focuses on recent human studies addressing the impact of depression on immune function, and the health consequences of those changes. **Results:** There is growing evidence that depression can directly stimulate the production of proinflammatory cytokines that influence a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, certain cancers, periodontal disease, frailty, and functional decline. Additionally, depression can down-regulate the cellular immune response; as a consequence, processes such as prolonged infection and delayed wound healing that fuel sustained proinflammatory cytokine production may be promoted by depression. **Conclusions:** These direct and indirect processes pose the greatest health risks for older adults who already show age-related increases in proinflammatory cytokine production. Thus, aging interacts with depression to enhance risks for morbidity and mortality.

Keywords: Proinflammatory cytokines; Interleukin 6; Psychoneuroimmunology; Stress

Depression is the most common psychiatric illness; both major depression and subthreshold depressive symptoms carry substantial health risks, reviewed in the articles in this issue of the journal and elsewhere [1–4]. Depression can affect health through many pathways; these influences may occur through health behaviors or compliance with medical regimens, as well as through alterations in the functioning of the central nervous system (CNS), immune, endocrine, and cardiovascular systems [5–8]. In this paper, we consider how depression may contribute to morbidity and mortality through immune dysregulation. We focus on a central immunological mechanism that serves as a gateway for a range of age-associated diseases, the dysregulation of proinflammatory cytokine production, particularly interleukin 6 (IL-6) [9].

Although we will not address the effects of disease on emotional distress in any detail, it is important to mention the bidirectional nature of the relationship. Unquestionably, cytokines have substantial effects on the CNS, including production and enhancement of negative moods, physical symptoms including lethargy and fatigue, and a range of sickness behaviors from shivering to loss of appetite [8,10,11]. Indeed, despite our focus on the impact of depression on immune responses and disease, there is also plausible evidence that the immune system has a role in the neuroendocrine and behavioral features of both depressive and anxiety disorders [8,11].

Morbidity, mortality, and aging: central immunological mechanisms

The immune system's inflammatory response can be triggered in a variety of ways, including infection and trauma. Inflammation is an important and constructive consequence of infection and injury; proinflammatory cytokines including IL-1, IL-6, and tumor necrosis factor (TNF) attract immune cells to the site of infection or injury, and prime them to become activated to respond. Anti-inflammatory cytokines such as IL-10 and IL-13 serve to dampen

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this immune response, including decreased cell function and synthesis of other cytokines. Thus, broadly speaking, cytokines provide intercellular signals that help to regulate the immune system's response to injury and infection.

Although the mechanisms associated with inflammation are critical to resolving infections and repairing tissue damage, chronic or recurring infections can provoke pathological changes [12]. For example, low levels of persistent inflammation may result when chronic infectious processes such as periodontal disease, urinary tract infections, chronic pulmonary disease, and chronic renal disease persistently stimulate the immune system. Persistent stimulation of proinflammatory cytokine production has the greatest impact among older adults who already show age-related increases in IL-6 production [13].

Depression and immune system alterations

Depression enhances the production of proinflammatory cytokines, including IL-6 [14–18]. Importantly, both depressive symptoms and syndromal depression are associated with heightened plasma IL-6 levels [16]. Following successful pharmacologic treatment, elevated IL-6 levels decline in patients with a major depression diagnosis [19]. Moreover, both physical and psychological stressors can provoke transient increases in proinflammatory cytokines [20–22]; in animal models, both stress and administration of epinephrine elevate plasma IL-6, consistent with evidence that IL-6 production is stimulated through β-adrenergic receptors, among other pathways [23,24]. Thus, production of IL-6 and other proinflammatory cytokines can be directly stimulated by negative emotions and stressful experiences, providing one direct pathway.

Overproduction of proinflammatory cytokines may lead to subsequent maladaptive immune and endocrine changes. IL-6 is a potent stimulator of corticotropin-releasing hormone (CRH) production, a mechanism that leads to heightened HPA activity, including elevated levels of plasma ACTH, followed by increased cortisol levels [14]; elevations in ACTH and cortisol can provoke multiple adverse immunological changes [8]. The complexity of these potential interactions is further underscored by one line of research which suggests that once cortisol levels rise, they can initiate, perpetuate or aggravate syndromal depression, depression-like behaviors, and depressive symptoms such as anxiety, insomnia, and poor memory [25]. Thus, negative emotions that dysregulate IL-6 secretion may also promote adverse neuroendocrine alterations.

Indeed, in addition to their association with enhanced secretion of proinflammatory cytokines, depression and distress can also have direct adverse effects on a variety of other immunological mechanisms, including the downregulation of cellular and humoral responses [8], and these changes are large enough to be clinically significant. For example, vaccine responses demonstrate clinically relevant alterations in immune responses to challenge under well-controlled conditions; accordingly, they serve as a proxy for response to an infectious agent [26–29]. More distressed and more anxious individuals produce immune responses to vaccines that are delayed, substantially weaker, and/or shorter lived [26–29]; as a consequence, it is reasonable to assume these same individuals would also be slower to develop immune responses to pathogens; thus, they could be at greater risk for more severe illness. Consistent with this argument, adults who show poorer responses to vaccines also experience higher rates of clinical illness, as well as longer lasting infectious episodes [30]. In addition, other researchers have shown that distress can alter susceptibility to cold viruses [31]. Furthermore, distress also provokes substantial delays in wound healing [32,33], and enhances the risk for wound infection after injury [34].

Increased susceptibility to infectious disease and poorer recovery from infection are substantial and important problems; in addition, however, they carry additional risks. Repeated, chronic, or slow-resolving infections or wounds enhance secretion of proinflammatory cytokines, a process that can serve to further inhibit certain aspects of immune responses (e.g., IL-2, a cytokine important in protection against infection) [35]. Thus, depression can directly affect the cells of the immune system and modulate the secretion of proinflammatory cytokines; in addition, depression may also contribute to prolonged or chronic infections or delayed wound healing, processes that indirectly fuel proinflammatory cytokine production. We next consider evidence which suggests that the etiology and course of a very broad range of diseases may be altered by dysregulated inflammatory responses.

Morbidity, mortality, and inflammatory immune responses

Inflammation has been linked to a spectrum of conditions associated with aging, including cardiovascular disease [9]. The association between cardiovascular disease and IL-6 is related in part to the central role that this cytokine plays in promoting the production of C-reactive protein (CRP), an important risk factor for myocardial infarction [23]. For example, high concentrations of CRP predicted the risk of future cardiovascular disease in apparently healthy men [36]. Further studies provided mechanistic links: chronic infections amplified the risk for development of atherosclerosis fourfold in subjects who were free of carotid atherosclerosis at baseline, conferring increased risk even in subjects lacking conventional vascular risk factors [37]. Indeed, the increased risk for artery-clogging plaque was greater than that conferred by elevated blood pressure or cholesterol [37]. Cardiovascular disease is the leading cause of death, and individuals with high levels of both IL-6 and CRP were 2.6 times more likely to die over a 4.6-year period than those who had low levels of both [38].

In addition to cardiovascular disease, inflammation has been linked to a spectrum of conditions associated with aging, including osteoporosis, arthritis, type 2 diabetes, certain lymphoproliferative diseases and other cancers (including multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia), Alzheimer's disease, and periodontal disease [9]. In fact, more globally, chronic inflammation has been suggested as one key biological mechanism that may fuel declines in physical function leading to frailty, disability, and, ultimately, death [12,39]. For example, elevated levels of CRP and IL-6 predicted the development of type 2 diabetes in a 4-year follow-up period in healthy women after adjustments for BMI, family history of diabetes, smoking, exercise, alcohol, and hormone replacement therapy; among women in the highest vs. lowest quartiles, the relative risk for developing diabetes was 7.5 for IL-6 and 15.7 for CRP [40].

In other work, elevated serum IL-6 levels predicted future disability in older adults, a finding that may reflect the effects of the cytokine on muscle atrophy, and/or to the pathophysiologic role played by the cytokine in particular diseases [41]. Proinflammatory cytokines including IL-6 may slow muscle repair following injury and accelerate muscle wasting [42]; indeed, IL-6 and CRP also play a pathogenic role in a range of diseases associated with disability among the elderly (osteoporosis, arthritis, and congestive heart failure, among others) [41]. In this context, it is interesting that IL-6 is also associated with self-rated health [43], a robust predictor of mortality [10]. Thus, the clinical importance of immunological dysregulation for older adults is highlighted by increased risks across diverse conditions and diseases.

Health behaviors

In addition to the direct influences of psychological states on physiological function, distressed individuals are more likely to have health habits that put them at greater risk, including poorer sleep, a greater propensity for alcohol and drug abuse, poorer nutrition, and less exercise, and these health behaviors have cardiovascular, immunological, and endocrinological consequences [44]. Higher plasma IL-6 and CRP levels are associated with adverse health habits: values for both are higher in smokers than nonsmokers, in individuals who report less physical activity, and in those with a higher body mass index [39,41]. However, health habits including smoking, physical activity, and alcohol use have typically explained only a small part of the excess mortality associated with depression among older adults [3]. Similarly, IL-6 has robust relationships with morbidity and mortality, even after controlling for health behaviors [39–41]. Thus, health behaviors, although obviously important, are not sufficient to explain the relationship between depression and disease.

Pharmacologic treatments hold promise. A prospective trial of statins produced reductions in CRP, providing evidence that these drugs have anti-inflammatory effects in addition to their ability to lower lipids [45]. Additionally, the use of antidepressants can normalize activation of the inflammatory response system in patients with a major depression diagnosis [19]. The question of whether cognitive or other psychological treatments for depression have similar positive consequences is an important arena for future research.

Conclusions

Many lines of evidence now indicate that IL-6 may function as a "…global marker of impending deterioration in health status in older adults" (p. 645) [41]. Indeed, even after the point at which risk factors such as cholesterol, hypertension, and obesity predict health deterioration less successfully among the very old, chronic inflammation continues to be an important marker [41]. We have argued that depression (both syndromal and subsyndromal) directly prompts immune dysregulation, and these processes may lead to subsequent maladaptive immune and endocrine changes [14,20–24]. Production of IL-6 and other proinflammatory cytokines can be directly stimulated by depression, providing one direct pathway. In addition, depression and stress may also contribute to prolonged infection or delayed wound healing, processes that fuel sustained proinflammatory cytokine production. Thus, research that addresses the dysregulation of the immune and endocrine systems associated with depression could substantially enhance our understanding of psychological influences on health, particularly among the elderly.

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EXHIBIT 20

Stress Weakens the Immune System

Friends, relaxation strengthen health.

What the Research Shows

Stressed out? Lonely or depressed? Don't be surprised if you come down with something. Psychologists in the field of "psychoneuroimmunology" have shown that state of mind affects one's state of health.

In the early 1980s, psychologist Janice Kiecolt-Glaser, PhD, and immunologist Ronald Glaser, PhD, of the Ohio State University College of Medicine, were intrigued by animal studies that linked stress and infection. From 1982 through 1992, these pioneer researchers studied medical students. Among other things, they found that the students' immunity went down every year under the simple stress of the three-day exam period. Test takers had fewer natural killer cells, which fight tumors and viral infections. They almost stopped producing immunity-boosting gamma interferon and infection-fighting T-cells responded only weakly to test-tube stimulation.

Those findings opened the floodgates of research. By 2004, Suzanne Segerstrom, PhD, of the University of Kentucky, and Gregory Miller, PhD, of the University of British Columbia, had nearly 300 studies on stress and health to review. Their meta-analysis discerned intriguing patterns. Lab studies that stressed people for a few minutes found a burst of one type of "first responder" activity mixed with other signs of weakening. For stress of any significant duration - from a few days to a few months or years, as happens in real life - all aspects of immunity went downhill. Thus long-term or chronic stress, through too much wear and tear, can ravage the immune system.

The meta-analysis also revealed that people who are older or already sick are more prone to stress-related immune changes. For example, a 2002 study by Lyanne McGuire, PhD, of John Hopkins School of Medicine with Kiecolt-Glaser and Glaser reported that even chronic, sub-clinical mild depression may suppress an older person's immune system. Participants in the study were in their early 70s and caring for someone with Alzheimer's disease. Those with chronic mild depression had weaker lymphocyte-T cell responses to two mitogens, which model how the body responds to viruses and bacteria. The immune response was down even 18 months later, and immunity declined with age. In line with the 2004 meta-analysis, it appeared that the key immune factor was duration, not severity, of depression. And in the case of the older caregivers, their depression and age meant a double-whammy for immunity.

The researchers noted that lack of social support has been reported in the research as a risk factor for depression, an insight amplified in a 2005 study of college students. Health psychologists Sarah Pressman, PhD, Sheldon Cohen, PhD, and fellow researchers at Carnegie Mellon University's Laboratory for the Study of Stress, Immunity and Disease, found that social isolation and feelings of loneliness each independently weakened first-year students' immunity.

In the study, students got flu shots at the university health center, described their social networks, and kept track of their day-to-day feelings using a handheld computer (a new technique called "momentary ecological awareness"). They also provided saliva samples for measuring levels of the stress hormone cortisol. Small networks and loneliness each independently weakened immunity to a core vaccine component. Immune response was most weakened by the combination of loneliness and small social networks, an obvious health stress facing shy new students who have yet to build their friendship circles.

What the Research Means

Emerging evidence is tracing the pathways of the mind-body interaction. For example, as seen with the college students, chronic feelings of loneliness can help to predict health status -- perhaps because lonely people have more psychological stress or experience it more intensely and that stress in turn tamps down immunity. It's also no surprise that depression hurts immunity; it's also linked to other physical problems such as heart disease. At the same time, depression may both reflect a lack of social support and/or cause someone to withdraw from social ties. Both can be stressful and hurt the body's ability to fight infection.

All of these findings extend what we know about how stress management and interpersonal relationships can benefit day-to-day health, doing everything from helping us combat the common cold to speeding healing after surgery. The research is in synch with anecdotal reports of how people get sick in stressful times, but understanding exactly *how* psychology affects biology helps scientists to recommend the best ways we can build up immunity.

How We Use the Research

Managing stress, especially chronic or long-term stress (even if it's not intense), may help people to fight germs. When burdened with long-term stressors, such as caring for an elderly parent or spouse with dementia, health can benefit from conscientious stress management.

Kiecolt-Glaser and Glaser confirmed this hopeful option by comparing the immune function of exam-stressed medical students given hypnosis and relaxation training with that of students without training. At first, the immune responses of the two groups appeared to both go down. However, closer inspection revealed that some students took this exercise more seriously than others. Those who didn't take relaxation training seriously didn't fare so well; those who practiced conscientiously did actually have significantly better immune function during exams than students who practiced erratically or not at all.

Finally, the newest findings on social stress underscore the value of good friends; even just a few close friends can help someone feel connected and stay strong. Social ties may indirectly strengthen immunity because friends - at least health-minded friends -- can encourage good health behaviors such as eating, sleeping and exercising well. Good friends also help to buffer the stress of negative events.

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Co-Morbidity of PTSD and Immune System Dysfunction: Opportunities for Treatment

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Abstract

Posttraumatic stress disorder (PTSD) is defined as a psychiatric disorder; however, PTSD co-occurs with multiple somatic manifestations. People living with PTSD commonly manifest dysregulations in the systems that regulate the stress response, including the hypothalamic-pituitary-adrenal (HPA) axis, and development of a pro-inflammatory state. Additionally, somatic autoimmune and inflammatory diseases and disorders have a high rate of co-morbidity with PTSD. Recognition and understanding of the compounding effect that these disease states can have on each other, evidenced from poorer treatment outcomes and accelerated disease progression in patients suffering from co-morbid PTSD and/or other autoimmune and inflammatory diseases, has the potential to lead to additional treatment opportunities.

Keywords

Post-traumatic stress disorder; PTSD; Autoimmune disease; Inflammatory diseases; Rheumatoid arthritis

Introduction

Although traditionally considered a type of anxiety disorder, post-traumatic stress disorder (PTSD) is classified as a Trauma and Stress related disorder in DSM-V. PTSD is a chronic psychiatric illness that develops subsequent to experiencing a significant traumatic event. Although exposure to a stressful event is required for PTSD, only a minority (8–18%) [1–3] of trauma exposed individuals go on to develop the disorder. DSM-V criteria for PTSD include delayed onset of behavioral changes that can be grouped into 4 distinct diagnostic clusters: re-experiencing, avoidance, hyper-arousal and negative cognitions and mood.

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PTSD is also a somatic condition, such that patients with PTSD have been found to have biological alterations in several primary pathways involving the neuroendocrine [4] and immune systems [5]. Much like physiological stress, chronic psychological stress stimulates the stress response pathways of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system leading to downstream release of glucocorticoids (GC) and catecholamines. Cortisol, which is the primary endogenous GC hormone in humans, acts on the central nervous system, metabolic system, and immune system to modulate the stress response. GCs impact physiology and behavior by binding to the intracellular GC receptor (GR) on target tissues leading to downstream effects of immunosuppression, increased energy metabolism, and negative feedback inhibition of the HPA axis. In this way, GC signaling is central to the neuroendocrine modulation of the immune system.

PTSD co-occurs with dysregulation of the HPA axis, impaired GC signaling, and the development of a pro-inflammatory state. Not surprisingly, PTSD is associated with poor self-reported physical health as well as high rates of comorbidities, such as cardiovascular, respiratory, gastrointestinal, inflammatory and autoimmune diseases [6–8]. Recently a large retrospective cohort study of 666,269 Iraq war veterans showed a two-fold increase in the risk of autoimmune diseases in individuals with PTSD compared to those without any psychiatric illness and a 51% increased risk when compared to individuals with other psychiatric illnesses [9]. Dysregulations in immune function as a result of the complex interplay between the neuroendocrine and immune systems in PTSD may unmask a predisposition to, or accelerate the progression of, autoimmune (AI)/inflammatory diseases, thereby compounding the disease burden in these patients. In the following sections we will review the mechanistic links between neuroendocrine and immune dysfunctions in PTSD and outline existing and novel pharmacological treatment options that may be able to address both the psychological and biological disturbances observed in patients living with PTSD.

Candidate Mechanisms Linking PTSD and Immune Dysfunction

Reduced Circulating Cortisol

As mentioned above, neuroendocrine alterations in people living with PTSD may precipitate immune disturbances. The dogmatic physiological signature of chronic stress is simultaneous elevations in concentrations of cortisol and catecholamines [5]. Contrary to this dogmatic view, PTSD is associated with low levels of morning cortisol and elevated levels of norepinephrine (NE). Excessive activation of the HPA axis in response to trauma and sustained increases in corticotrophin-releasing factor (CRF) are collectively proposed to downregulate CRF receptors in the pituitary leading to downstream reduction in GC signaling, decreased secretion of cortisol, and subsequently increased GC sensitivity [10]. These changes, along with enhanced sympathetic activity driven stimulation of β2-adrenergic receptor on immune cells, may lead to increased cytokine production, fostering the hyper-inflammatory state frequently co-morbid with PTSD.

An alternative view is that low cortisol concentrations are a precipitator of PTSD rather than a consequence of PTSD. Low salivary and urinary cortisol immediately following trauma have been reported to be predictors of PTSD suggesting that low cortisol concentrations may

in fact be a preexisting vulnerability for developing PTSD rather than a consequence of PTSD [11]. Interestingly, inadequate cortisol secretion in relation to the chronic inflammation observed in rheumatoid arthritis, suggests that the suboptimal production of cortisol may be involved in onset and/or progression of autoimmune disease [12,13]. Hence, overlap may exist between the mechanisms by which low cortisol concentrations may precipitate both psychiatric and somatic diseases and disorders.

However, because of the multifaceted regulation and impact of the GR, information about glucocorticoids alone is not consistently predictive of their function or dysfunction. GRs have extensive variability in their actions depending on the target tissue. Multiple independent promoters present in the GR gene contribute to GR variability by influencing tissue specificity of GR gene expression. Epigenetic modulation of some of these promoters has been demonstrated to change GR gene expression and function in PTSD [14]. Moreover, single nucleotide polymorphisms in the GR gene NR3C1 and the FKBP5 gene (co-chaperone of hsp90 which regulates GR sensitivity) are associated with altered HPA axis sensitivity (GR hypersensitivity or GR resistance) [15]. Hence, alterations in multiple factors including GR expression levels, GR affinity, co-factors, GR heterogeneity and GR density in target tissues are sufficient to affect GC signaling and are candidate mechanisms for enhanced inflammation associated with PTSD.

Chronic Low Grade Inflammation

PTSD is linked to cytokinemia and a recent meta-analysis of 20 studies found increased plasma levels of pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β) & interleukin-6 (IL-6) in individuals with PTSD compared to healthy controls [16]. In addition, there is a prospective association of plasma C-reactive protein (CRP) concentrations with the development of PTSD [17], and higher mitogen induced cytokine production in trauma exposed soldiers correlates with augmentation of PTSD symptoms in response to subsequent stressors [18]. These findings suggest that inflammation may predispose an individual to PTSD, and inflammation may even form the biological basis of stress sensitization [18] that precipitates PTSD after trauma exposure.

The relationship between the HPA axis and cytokines is bidirectional. In addition to the previously discussed effects of the HPA axis on cytokines, cytokines can influence HPA axis signaling and impair cellular processes by stimulating oxidative stress. The sequela that follows cytokine-induced changes in the HPA axis and central nervous system has been proposed to lead to the manifestation of PTSD symptoms [19]. This proposition is consistent with results of a study using the predator exposure animal model of PTSD that demonstrated elevated levels of pro-inflammatory cytokines and reactive oxygen species in the brain (hippocampus, amygdala, pre-frontal cortex) and in the periphery as a consequence of stressor exposure [20]. Conversely, administration of the anti-inflammatory agent minocycline following a laboratory stressor is sufficient to block the development of PTSD-like behaviors in a rodent model [21].

Chronic inflammation is a pathological feature of multiple somatic diseases that are highly co-morbid with PTSD including cardiovascular disease, rheumatoid arthritis, asthma, psoriasis, metabolic syndrome, fibromyalgia, chronic pain syndromes and hypothyroidism.

Common cytokines implicated in enhanced inflammation in PTSD and other diseases may therefore serve as a potent therapeutic target in the treatment of both types of conditions.

Alterations in Innate and Adaptive Immunity

A burgeoning area of study is the relationship between PTSD and innate and adaptive immunity. A recent study of U.S. Marines applied weighted gene co-expression network analysis to RNA-Seq and microarray assessment of peripheral blood leukocyte gene expression taken pre- and post-deployment. The authors reported that PTSD risk and PTSD cases groups both had enhanced differential expression of genes associated with innate immune responses mediated by interferon signaling. These findings add to the authors previous work showing that differential expression of CRP and genes involved in antiviral interferon response were associated with the risk of developing PTSD [22] and suggest that innate immunity up-regulation may be both a risk for, and consequence of, PTSD.

A relationship between PTSD and adaptive immunity is also plausible given that cytokines drive differentiation of T cell subsets, and individuals living with PTSD exhibit elevated cytokine production. To this end, a recent study demonstrated an association between PTSD and a T cell phenotype consistent with increased differentiation of T cells and interpreted as early aging of the immune system [23]. Furthermore, T cells may provide a window into the susceptibility of an individual to psychiatric disorders such that responsiveness of T cells to the synthetic GC dexamethasone prior to military deployment predicted both PTSD and depression following deployment [24]. Collectively, the shifts in T cell biology observed in PTSD push towards a preponderance of CD4+ T helper 1 (Th1) cells over the C4+ T helper 2 (Th2) type cells which correlates with increased plasma levels of Interferon-gamma (IFN-γ) in PTSD [25]. Although mechanisms have not been elucidated to date, Marpe Bam et al., has shown that epigenetic modifications and miRNAs were associated with elevated gene expression of the pro-inflammatory cytokine interleukin-12 (IL-12) in peripheral blood mononuclear cells (PBMCs) of PTSD patients [26]. In addition to PTSD, several autoimmune diseases are associated with alterations of the Th1 versus Th2 cytokine balance including rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and autoimmune thyroid disease. In these somatic conditions, the balance is skewed towards Th1 and an excess of IL-12 and TNF-α production, whereas Th2 and production of anti-inflammatory interleukin-10 (IL-10) appear to be deficient [12].

In addition to shifts in T helper cells, Jergovic et al., found a ~50% decrease in the number of regulatory T cells (T_{reg}) in PTSD patients compared to healthy controls [27]. T_{reg} are essential for controlling immune responses and maintaining self-tolerance by inhibiting auto reactive T cells. A decrease in number and function of peripheral T_{reg} has been associated with the development of multiple autoimmune diseases that are highly co-morbid with PTSD [28].

Telomere Shortening and Premature Immunosenescence

In addition to elevated levels of terminally differentiated T cells and an altered Th1/Th2 balance, PTSD has been associated with the age-related phenomenon of telomere shortening. Chronic inflammation has been shown to accelerate telomere shortening leading

to cellular aging and premature senescence that have been implicated in loss of control of the immune system [29]. Senescent cells are terminally differentiated and no longer fully functional, but instead of undergoing cell death, they exist in a zombie-like state spewing cytokines into the cellular milieu. Telomere shortening has been identified in many autoimmune diseases [30] and is associated with acceleration of the manifestation of age-related diseases. Telomere shortening of leukocytes/PBMCs has emerged as a biomarker of PTSD and a recent literature review of 32 studies between 2001 and 2014 found reduced leukocyte telomere length and increased pro-inflammatory markers in PTSD patients suggesting early immunosenescence [23]. Additionally, PTSD is associated with earlier onset of age-related conditions linked to telomere shortening and increased mortality [31].

Sex Differences and PTSD

Similar to other neuropsychiatric and somatic disorders, sex differences have been reported in the context of PTSD. There are well-known differences in PTSD risk between men and women with women exhibiting a higher frequency of PTSD than men (2:1)[33], not explained solely on the basis of exposure type and/or severity alone. Dias et. al demonstrated that female-specific elevation of pituitary adenylate cyclase-activating peptide (PACAP) and differential methylation of a single nucleotide polymorphism (rs2267735) on the PACAP gene (Adcyap1r1) was associated with a PTSD diagnosis in females, but not in males [32]. Differences in the neuroendocrine response to stress in males and females can be attributed to genomic (as above) or hormonal differences to the neuroendocrine response to stress between the sexes [34].

Additionally, autoimmune diseases disproportionally impact females over males, reflected in the study conducted by O'Donovan et al., showing that women with PTSD were three times more likely to be diagnosed with an autoimmune condition [9]. Interestingly however, the magnitude of PTSD-related increased risk was similar between the sexes and the authors therefore did not find a sex difference in the relative risk of autoimmune diseases in PTSD patients. They did however find that a history of Military Sexual Trauma (MST) and PTSD were associated with the highest risk of autoimmune diseases in both men and women and thus MST was an independent risk factor in the development of autoimmune disease. Notably, the patient populations in a large majority of studies referenced in this paper are composed of combat veterans exposed to the trauma of war. But the finding of MST as an independent risk factor for the development of PTSD points to the possibility that the type of trauma may correlate with severity and/or risk of autoimmune or somatic illness, and warrants further work in this area.

PTSD Treatment Opportunities: Immune System Intervention

The literature summarized here establishes that in addition to the commonly appreciated psychiatric manifestations of PTSD, marked alterations in the neuroendocrine and immune systems exist in individuals living with PTSD. As such, intervention strategies that target neuroendocrine and immune dysfunction may prove beneficial to the treatment of PTSD. A similar angle has been assessed in the context of depression such that a meta-analysis illustrates that elevations in CRP and IL-6 precede development of depression and that

patients with increased inflammation are less likely to respond to conventional anti-depressants and more likely to respond to adjunctive anti-inflammatory treatment [35].

Although mechanistically interventions that target function of the HPA axis and/or GR should prove effective in the treatment of both PTSD and immune dysfunction, these neuroendocrine interventions have had mixed utility which may be due to the pervasive nature of the GR on multiple organ systems. Mifepristone, a GR antagonist, has been reported to effectively improve metrics of PTSD symptoms [36], but a more recent report from the same research group demonstrates improvements in cognition but not in symptoms of PTSD or metrics of physical health [37]. More targeted treatment of GR function, through manipulation of GR co-chaperones such as FKBP5, may be a more advantageous route of intervention given that this type of intervention should leave non-pathological GRs intact [38]. To this end, studies of rapamycin, a drug which, among other things, can alter function of GR co-chaperones, has shown promise in rodent models of PTSD [39] and is already FDA approved and in clinical trials unrelated to PTSD.

Given the potential limitations to interventions at the level of GR and the HPA axis, attention to immune-centric interventions is also warranted. Several pro-inflammatory cytokines elevated in PTSD are also implicated in autoimmune diseases and therefore are uniquely positioned to function as biomarkers for diagnosis and treatment of both conditions. For instance, plasma levels of IL-1β and IL-6 have been shown to positively correlate with PTSD symptom duration and severity respectively [16], and can therefore be used to monitor treatment response in PTSD. Drugs aimed at decreasing concentrations of pro-inflammatory cytokines in the circulation might have dual benefits and help ease disease burden in PTSD patients. Canakinumab, a monoclonal antibody against IL-1β, and anakinra, an IL-1 receptor antagonist, are two such medications that target IL-1β. These drugs have been used in the treatment of rheumatoid arthritis and other inflammatory conditions with positive results [40]. Clazakizumab, a monoclonal antibody against IL-6, is in phase 2 clinical trials to treat rheumatoid arthritis with promising results [41]. Furthermore, in rheumatoid arthritis patients, long term treatment with anti-TNF agents has been shown to raise cortisol levels (inadequate cortisol in relation to inflammation implicated in chronic low-grade inflammation) and normalize the HPA axis leading to rapid clinical improvement [42].

In addition, targeting senescent cells may be an advantageous point of intervention. Senolytics are a new intervention strategy in aging research and in diseases of aging which show particular promise. These treatments target and remove the senescent cells, many of which are believed to contribute to cytokinemia, without damaging healthy cells. This exfoliation of the immune system may confer benefits for both traditional immune disorders and neuropsychiatric disorders with an immune component. Although initial studies used methods for clearance of senescent cells that lacked translational potential, recent work demonstrates successful administration of a pharmacological senolytic agent in a mouse model [43].

In addition to these novel immune-driven interventions, it is important to recognize that some of the existing treatments for PTSD confer immune benefits. SSRIs are first line treatment of PTSD, and have been shown to exert anti-inflammatory effects on T-

lymphocytes, dendritic cells, and neutrophils [44]. Specifically fluoxetine and citalopram were found to exhibit an anti-arthritic effect on murine collagen-induced arthritis and in a human *ex vivo* disease model of rheumatoid arthritis [45]. The anti-inflammatory effect of SSRIs in human rheumatoid arthritis tissue was due to reduction of spontaneous cytokine production from macrophages (IL-6, INF-γ and IL-10) through toll-like receptors. Previous studies have found SSRIs to improve symptoms in encephalomyelitis, a multiple sclerosis model through reduction in pro-inflammatory cytokines [46–48]. Other drugs used in the treatment of PTSD that have been found to have anti-inflammatory effects include prazosin (alpha-1-adrenoreceptor blocker) and ketamine. Prazosin has been shown to be effective in treatment resistant cases of PTSD in which recurrent nightmares are problematic [49]. Previous studies have found prazosin and doxazosin, also an alpha-1 blocker, to exhibit anti-inflammatory effects in rodent models of inflammation by inhibiting the production of lipopolysaccharide induced pro-inflammatory cytokines TNF-α and IL-1β [50,51]. Ketamine infusion has been shown to have a rapid reduction in symptom severity in patients with chronic PTSD [52] and ketamine possesses anti-inflammatory actions which have been attributed to inhibition of transcription factors activator protein-1 and nuclear factor (NF)-κB, as well as lowering of serum levels of IL-6, TNF-α, inducible nitric oxide synthase and CRP [53].

Conclusions

Although once believed to be an immune-privileged site, the bidirectional communication between the brain and periphery is now commonly appreciated. The growing recognition that neuropsychiatric disorders are also somatic disorders will improve understanding of disease pathogenesis and lead to advances in treatment options. In the case of PTSD, the relationship with the immune system appears to be multi-tiered and bidirectional. Continued monitoring of developments in immunological interventions and efforts to apply these interventions to PTSD is essential to advancing biological psychiatry. Furthermore, given the bidirectional nature of the relationship between PTSD and immune system function, recognition and treatment of PTSD may improve immunological outcomes for individuals living with primary disorders of the immune system.

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Highlights

- PTSD co-occurs with somatic diseases.
- PTSD is commonly associated with neuroendocrine and immune dysfunction
- Targeting neuroendocrine and immune dysfunction may improve PTSD symptoms.
- Targeting PTSD may improve somatic co-morbidities.
- Translational reciprocity between biological psychiatry and immunology may advance treatment options.

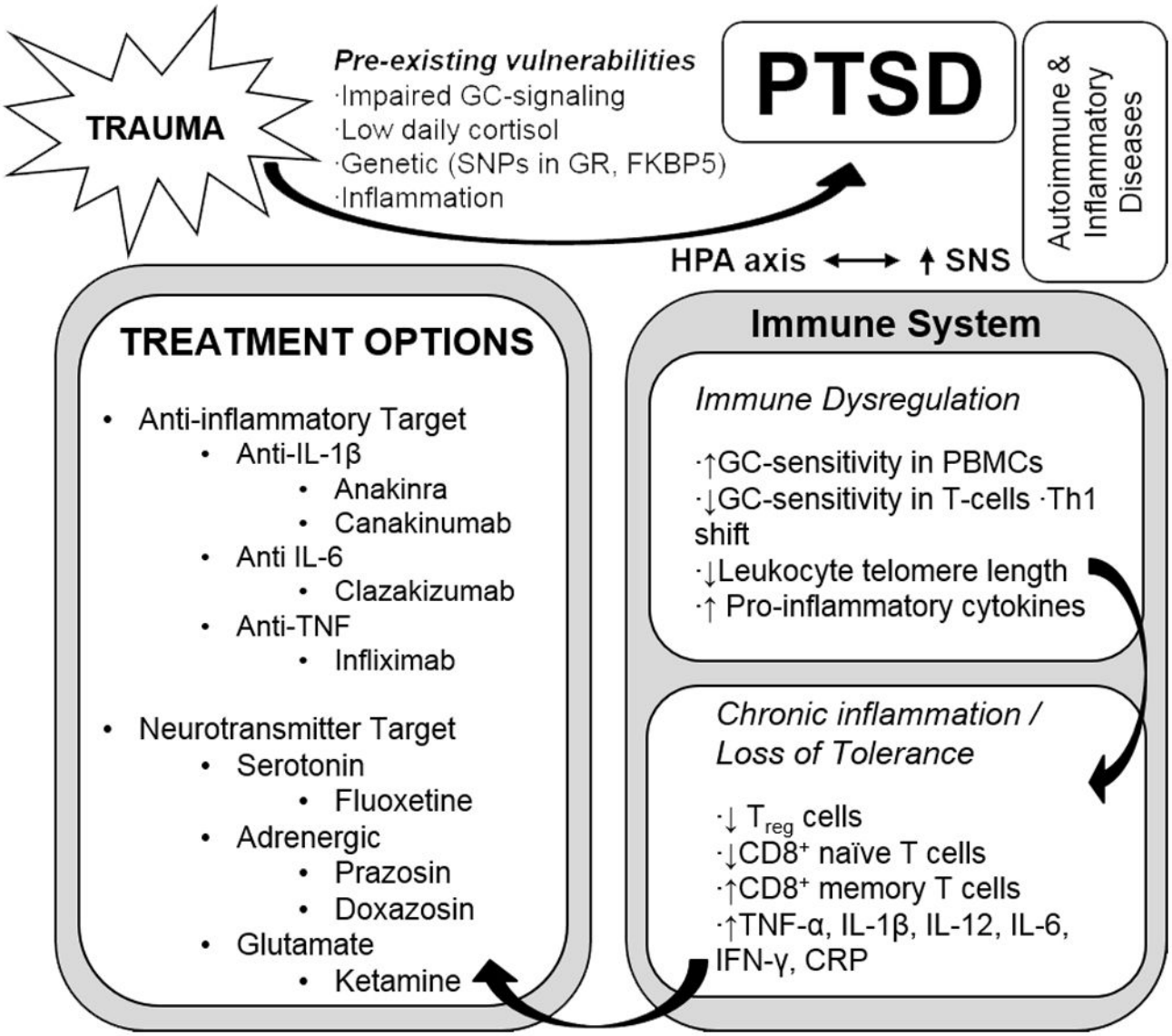

Figure 1. A Psychoneuroimmunological Model of PTSD

Exposure to severe psychological trauma in the presence of pre-existing risk factors leads to PTSD. Immune system changes in PTSD include altered glucocorticoid (GC) sensitivity in target immune cells, shifts in immune cell distribution, immunosenescence, elevated pro-inflammatory cytokines and a decrease in regulatory T cells. A complex interplay of the biological alterations in the stress response known to exist in PTSD, along with immune alterations, are hypothesized to increase the risk for co-morbid somatic autoimmune and inflammatory disorders. Immune interventions may improve both primary PTSD symptoms and co-morbid somatic disorders related to the immune system.

EXHIBIT 22

META-ANALYSIS

A Systematic Review of Mortality in Schizophrenia

Is the Differential Mortality Gap Worsening Over Time?

Sukanta Saha, MSc, MCN; David Chant, PhD; John McGrath, MD, PhD, FRANZCP

Context: Despite improvements in mental health services in recent decades, it is unclear whether the risk of mortality in schizophrenia has changed over time.

Objective: To explore the distribution of standardized mortality ratios (SMRs) for people with schizophrenia.

Data Sources: Broad search terms were used in MEDLINE, PsychINFO, Web of Science, and Google Scholar to identify all studies that investigated mortality in schizophrenia, published between January 1, 1980, and January 31, 2006. References were also identified from review articles, reference lists, and communication with authors.

Study Selection: Population-based studies that reported primary data on deaths in people with schizophrenia.

Data Extraction: Operationalized criteria were used to extract key study features and mortality data.

Data Synthesis: We examined the distribution of SMRs and pooled selected estimates using random-effects meta-analysis. We identified 37 articles drawn from 25 different nations. The median SMR for all persons for all-cause mortality was 2.58 (10%-90% quantile, 1.18-5.76), with a corresponding random-effects pooled SMR of 2.50 (95% confidence interval, 2.18-2.43). No sex difference was detected. Suicide was associated with the highest SMR (12.86); however, most of the major causes-of-death categories were found to be elevated in people with schizophrenia. The SMRs for all-cause mortality have increased during recent decades ($P=.03$).

Conclusions: With respect to mortality, a substantial gap exists between the health of people with schizophrenia and the general community. This differential mortality gap has worsened in recent decades. In light of the potential for second-generation antipsychotic medications to further adversely influence mortality rates in the decades to come, optimizing the general health of people with schizophrenia warrants urgent attention.

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IT IS NOW WIDELY ACKNOWLEDGED that schizophrenia contributes substantially to the global burden of disease.[1,2] It is also well known that schizophrenia is associated with elevated suicide rates.[3] Less widely appreciated is the fact that people with schizophrenia are at increased risk for premature death associated with comorbid somatic conditions.[4] Apart from adverse effects related to medication, schizophrenia can trigger a cascade of socioeconomic and lifestyle factors that, in turn, can translate into adverse physical health outcomes. These comorbid physical conditions contribute to increased mortality risks among people with schizophrenia.

The association between severe mental illness and increased mortality rates has long been recognized.[5] With respect to the group of disorders now labeled schizophrenia, increased mortality rates have been the object of scrutiny since the early 20th century.[6-8] The quality of research on this topic has improved greatly in recent decades, with access to larger, better-characterized samples and the availability of high-quality mortality data for the general population. Access to these data allows the calculation of the standardized mortality ratio (SMR), which compares mortality in people with schizophrenia vs the general population. The SMRs are calculated by dividing the observed mortality rates in a given population (eg, the number of deaths in a group of individuals with schizophrenia) by the expected mortality rates in that same group as predicted by age- and sex-specific mortality rates for a standard population. Thus, an SMR of 2.0 would indicate that people

with schizophrenia are twice as likely to die compared with the general population. The SMRs can be calculated for overall mortality (all-cause) or for more specific, widely used categories (eg, cancer, cardiovascular disease, endocrine disorders, or suicide).

In recent years, several scholarly reviews[4,9-11] have noted higher mortality in schizophrenia compared with the general population. A meta-analysis,[4] based on 18 studies published between 1969 and 1996, reported an all-cause SMR for people with schizophrenia of 1.51. Another meta-analysis,[11] based on 20 studies published between 1973 and 1995, reported a similar SMR for people with schizophrenia (1.57). Although these 2 systematic reviews agreed on the size of the pooled SMR associated with schizophrenia, there were discrepancies in the sex difference of overall mortality ratios. Brown[4] found a small but significant male excess in the overall mortality ratio, whereas other studies[12,13] reported either no sex difference[11] or higher mortality ratios in females compared with males.

In collating data from different sites, systematic reviewers need to appreciate the structure of the underlying data. In light of the differing population age structure and disease profile among sites,[1,14] we would expect substantial variation in mortality ratios among sites. For example, one would predict that SMRs for people with schizophrenia would differ between developed and developing nations, where the profiles of disease and the access to services vary markedly.

Because of the increased focus on mental health care seen in many countries during the last few decades, one might predict that SMRs associated with disorders such as schizophrenia should be decreasing over time.[15,16] However, several authors have suggested that SMRs in schizophrenia have been increasing during recent decades. For example, Osby et al[17] found a linear increasing trend of mortality during 5-year periods from 1976 to 1995 among people with schizophrenia. The meta-analysis by Brown[4] also reported significantly higher mortality in the 1980s compared with the 1970s. Deinstitutionalization may have influenced recent secular changes in mortality rates in schizophrenia. Although deinstitutionalization started in the 1950s, findings on its relationship to mortality have been inconsistent.[10,11,18]

The aims of this study were to undertake a systematic review of mortality in schizophrenia and to examine a limited number of planned sensitivity analyses. In keeping with our previous systematic review of the incidence[19] and prevalence[20] of schizophrenia and considering that variability is to be expected in systematic reviews of SMRs,[4,21] we sought to preserve the expected variation in the data rather than to focus only on pooled values derived from meta-analysis. Thus, for the main analyses, we present distributions of mortality estimates with measures of central tendency (eg, median or means) and quantiles (10% and 90% quantiles). On the basis of all-cause SMR, we predicted that the SMRs of males and females would not differ significantly. We also predicted that SMRs from the developed world would differ from those from the developing world (nondirectional hypothesis). We wished to explore the impact of study quality on SMRs. With the assumption that higher-quality studies would be more likely to identify deaths in schizophrenia, we predicted that SMRs derived from such studies would be higher compared with those from lower-quality studies. On the basis of previous systematic reviews and commentaries, we predicted that SMRs would increase over time.

METHODS

DATA SOURCES

Most mortality studies are based on record linkage. People with schizophrenia are identified via psychiatric case registers and then subsequently linked to registers of cause of death. Some studies[13,22] report mortality ratios based on hospital inpatient cohorts. Other studies[23,24] have used community-based follow-up data for people with schizophrenia who are first identified through community surveys and then followed up for extended periods.

IDENTIFICATION OF STUDIES

Guidelines outlined by the Meta-analysis of Observational Studies in Epidemiology[25] were followed to identify and collate mortality studies. The broad search string of (*schizo* or psych**) and (*mortality or outcome or follow-up*) was used in MEDLINE, PsychINFO, Web of Science, and Google Scholar to identify all research studies that investigated mortality in schizophrenia. Potentially relevant articles (in all languages) were accessed to review the full text. Citations from significant articles and review articles were scrutinized to locate additional relevant articles, book chapters, and conference papers. The Web of Science Cited Reference Search system was also used to locate relevant articles. Finally, letters or e-mails were sent to the senior authors of articles that met the inclusion criteria. These authors were provided with an interim list of included studies and asked to nominate missing studies.

INCLUSION AND EXCLUSION RULES

Studies were included if they met all the following criteria: (1) published and/or available between January 1, 1980, and January 31, 2006, (2) reported deaths in people with schizophrenia as diagnosed by any criteria, (3) studied a population 15 years and older, (4) reported primary data on all-cause mortality and/or cause-specific mortality, and (5) reported SMRs and/or data on observed and expected deaths sufficient to calculate SMRs. Studies were excluded if they (1) involved people with a diagnosis other than schizophrenia (ie, studies that reported on broader categories of psychosis were excluded), (2) reported duplicate data, (3) reported SMRs solely attributable to suicide (this was the focus of a recent systematic review and meta-analysis[3]), and (4) reported mortality in subgroups of the population (eg, homeless people,[26] twins,[27] and those involved in clinical trials).

DATA ABSTRACTION

Once a study was included, data were extracted and entered into a 3-level, normalized database that included study-level variables (eg, authors, year of publication, and site), middle-level variables (eg, age group, recruitment duration, case-finding method, and diagnostic criteria), and estimate-level variables (eg, general and specific-cause SMRs for all persons, males, or females). Two or more of the authors checked all data used in the analysis. When disagreements arose, these were re-

solved by consensus. If required, we contacted the original authors for clarification of issues. The full data set is available from the authors (www.qcmhr.uq.edu.au/epi).

To assess the impact of overall quality of the distribution of SMRs, we devised a quality score. On the basis of operationalized criteria, this score rewarded studies that (1) used superior research design features (eg, more thorough case ascertainment, published diagnostic criteria, methods to confirm diagnosis, and longer periods of follow-up) and (2) provided comprehensive reporting of the study results (eg, provision of numerator, denominator, SMRs, details of subject attrition, and description of the completeness of the data source). Full details of the quality score used in this review are available from the authors (www.qcmhr.uq.edu.au/epi).

In systematic reviews, it is important to avoid double counting of the index variable (deaths) by the same or different studies. Thus, a key feature of this review is the application of sequential filters to identify discrete mortality estimates. We applied a similar sorting algorithm to that used in our previous reviews of schizophrenia.[19,20] Briefly, the mortality estimates were sorted into different causes of death. Study-level and middle-level filters were applied to isolate data from multiple studies that overlapped in both time and place. The third filter was used to select 1 representative mortality estimate for inclusion in the cumulative distribution using the "most informative" rule. For example, if 1 study presented multiple overlapping ratios, the ratios based on the largest sample were preferred (ie, the widest age range was preferred over narrower age strata).

The highest-order (and most reliable) category of death, all-cause mortality, can be further subdivided according to rules such as those codified by the *International Classification of Diseases, Ninth Revision (ICD-9)*.[28] Almost all included studies in this review were coded with the *ICD-9*. Although death can result from the combination of many different health problems, in circumstances in which several codes may be suitable, emphasis is given to the underlying cause of death. More specific causes of death can be allocated to categories according to organ systems (eg, cardiovascular or gastrointestinal) or nature of disease (eg, cancers are coded together). Apart from codes for these specific domains, studies occasionally report SMRs for middle-level categories such as all-unnatural (*ICD-9* codes E800-E999) (which includes codes for suicide, accident, and homicide) and all-natural (*ICD-9* codes 001-799; the remainder from all-cause when all-unnatural cause is excluded).

The SMRs were extracted from the publications or calculated by dividing the sum of observed deaths by the sum of expected deaths (when sufficient data were available to calculate these). The distributions of SMRs were assessed in cumulative plots, with every SMR contributing to the distribution. The distribution of the data was assessed in rank order for SMRs (lowest to highest ranks) with the cumulative percentage of SMRs shown on the vertical axis. Key features of these distributions are presented (eg, median, mean, geometric mean, standard deviation, and quantiles at 10%, 25%, 50%, 75%, and 90%).

For all-cause death, we were often able to extract data on case fatality rate (CFR). The CFR is calculated by dividing the number of deaths in people with schizophrenia during a certain period by the number of people with that disorder at the beginning of the period. An annualized CFR was derived to allow comparisons among studies of different durations.[14]

In keeping with definitions from our previous systematic reviews of schizophrenia,[20,29] we divided studies according to the per capita gross national product of the study site (based on 2004 data)[30] and used a standard World Bank definition of country status[31]: (1) least developed countries, mean income of less than US $2995; (2) emerging economy countries, mean income between US $2995 and $9266; and (3) developed countries, mean income of greater than US $9266.

To assess secular trends, we used meta-regression to examine the relationship between the midpoint of the follow-up period and all-cause SMR for persons. Study quality scores were divided into tertiles, and the distribution of all-cause SMR for persons were compared according to these 3 levels.

We performed statistical analyses for the test of significance between distributions of different SMRs. These analyses take into account (1) the need to control for within-study variation (estimates drawn from the same study tend to be more alike than SMRs drawn from different studies) and (2) the use of a log transformation to analyze distributions that are often positively skewed. Analyses were performed with SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

We also undertook a secondary analysis based on conventional meta-analytic techniques. Because SMRs are known to vary widely among sites because of population and disease frequency differences, we adopted a random-effects model to estimate a pooled SMR for all-cause mortality for persons.[21] When necessary, 95% confidence intervals (CIs) were generated according to the formula detailed by Rothman and Greenland.[21] Heterogeneity among the studies was tested using the Cochran heterogeneity statistic.[32] Apart from the specific analyses related to sex differences, we restricted the analyses to persons to limit the number of planned comparisons. The funding source played no part in the design, analyses, writing, or submission of this study.

RESULTS

The electronic search identified 1726 articles, whereas manual reference checking identified an additional 26 references. We received responses from 16 authors, who provided an additional 11 references. Four articles from languages other than English were included after translation. Eleven studies[33-43] were excluded because they completely overlapped with other included studies. Further details of the results of the search strategy and key features of the included studies are available from the authors (www.qcmhr.uq.edu.au/epi).

The systematic review identified 37 studies[9,12,13,18,22-24,44-73] that provided data on 561 SMRs for different causes of deaths drawn from 25 different countries: Australia (n=2),[59,68] Brazil (n=1),[61] Bulgaria (n=1),[53] Canada (n=3),[50,51,65] China (n=1),[53] Columbia (n=1),[53] Czech Republic (n=1),[53] Denmark (n=2),[63,64] Finland (n=3),[18,22,23] France (n=2),[46,48] Germany (n=1),[57] Hong Kong (n=1),[53] India (n=2),[12,53] Indonesia (n=1),[58] Ireland (n=2)[53,62] Israel (n=1),[73] Italy (n=2),[60,67] Japan (n=3),[53,69,71] Norway (n=1),[52] Russia (n=1),[53] Sweden (n=2),[9,66] Taiwan (n=1),[49] the Netherlands (n=1),[13] the United Kingdom (n=5),[44,47,53,54,56] and the United States (n=6).[24,45,53,55,70,72] The SMRs were based on an estimated total of 22 296 discrete deaths. Thirty-seven studies[9,12,13,18,22-24,44-73] provided SMRs for all-cause mortality for either all persons, males, or females.

Figure 1 shows the distribution for all-cause SMRs for all persons, males, and females. The median all-cause SMR for all persons (based on 38 SMRs) was 2.58, with 10% and 90% quantiles ranging from 1.18 to 5.76 (**Table 1**). In other words, people with schizophrenia had 2.5 times the risk of dying compared with the general population, and the central 80% of all SMRs varied over a 4-fold range. The median annualized all-cause CFR for all persons was

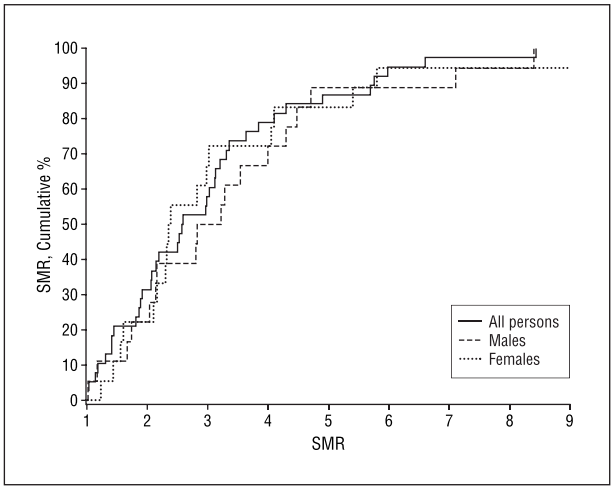

Figure 1. Cumulative plots of standardized mortality ratios (SMRs) for all-cause mortality associated with schizophrenia by sex.

95.4 per 10 000 population, with 10% and 90% quantiles ranging from 57.2 to 301.7 (5-fold range).

The median all-cause SMR for males (3.02) was slightly higher than females (2.37); however, these 2 distributions were not statistically significantly different ($F_{1,18}$=0.0003; P=.99). For all persons, the median SMR for natural causes of death was 2.41, and the 10% and 90% quantiles ranged from 0.99 to 4.10 (Table 1). Elevated median SMRs were found in all of the specific causes of death apart from cerebrovascular diseases.

Seven studies[18,47,49,51,56,65,66] published data for the summary category of unnatural causes of death for all persons, males, or females. Table 1 gives the distributions of SMRs for unnatural causes of death. People with schizophrenia had 12 times the risk of dying of suicide compared with the general population (median SMR, 12.86).

Twenty-two studies* were identified that contributed 28 SMRs for developed countries, 3 studies[53,58,61] contributed 6 SMRs for emerging economy countries, and 1 study[53] contributed 4 SMRs for least developed countries. When divided according to this criterion, the all-cause SMR distributions were not significantly different ($F_{2,34}$=0.30; P=.74); the median all-cause SMRs for least developed, emerging economy, and developed countries were 2.02, 2.19, and 2.79, respectively (**Table 2**).

When the all-cause SMRs for all persons were divided into study quality score tertiles, no significant differences were found between SMR distributions ($F_{2,24}$=0.61; P=.55). On the basis of follow-up periods, we identified 8 studies[24,45,51,54,55,63,71,72] with SMRs from the 1970s, 10 studies[47,53,57-60,65-67,73] with SMRs from the 1980s, and 7 studies[22,46,48,53,61,62,68] with SMRs from the 1990s. Concerning secular change, meta-regression confirmed a significant positive association between the follow-up period midpoint year and all-cause SMR (slope coefficient, 0.06; 95% CI, 0.01-0.11; z=2.21; P=.03). The median SMRs for the 1970s, 1980s, and 1990s were 1.84, 2.98, and 3.20, respectively. Concerning CFRs, the median rates per 10 000 population (all-cause mortality) were 162.2, 95.4, and 108.3 for the 1970s, 1980s, and 1990s, respectively. The CFRs for the 3 decades were not statistically significantly different ($F_{2,23}$=0.38; P=.38).

The 38 studies that report all-cause SMRs for all persons are shown in a traditional forest plot with a pooled estimate based on a random-effects model in **Figure 2**. Using traditional meta-analytic techniques, we found that the pooled random-effects all-cause SMR (based on 37 SMRs with finite standard errors) for all persons was 2.50 (95% CI, 2.18-2.83). The Cochran Q test found a marginally acceptable level of heterogeneity (Q_{36}=50.72; P=.06). We undertook several post hoc analyses to explore potential sources of variation (eg, published vs unpublished diagnostic criteria, cohorts based on first-episode patients vs all patients, cohorts based on inpatient and/or outpatient samples, sites clustered according to World Health Organization regions, and SMRs attributable to suicide sorted by decade). However, none of the post hoc comparisons resulted in significantly different SMR distributions (data not shown).

*References 22, 24, 45-48, 51, 53-55, 57, 59, 60, 62, 63, 65-68, 71-73.

COMMENT

People with schizophrenia have a substantially increased risk of death compared with the general population. Overall, people with schizophrenia have 2.5 times the risk of dying. This review was able to extract data from 37 studies that were conducted in 25 countries. As predicted, the distribution of all-cause SMRs showed prominent variability.

Confirming the hypothesis that the relative mortality risk associated with schizophrenia is increasing, we found that SMRs have increased in a linear fashion during the 3 decades examined in this study. This finding is consistent with earlier studies.[4,17] Considering that (1) CFRs for schizophrenia did not significantly differ among the decades and (2) age-standardized mortality rates are generally decreasing in most nations,[74-76] these findings suggest that people with schizophrenia have not fully benefited from the improvements in health outcomes available to the general population. The SMRs are ratio measures and thus reflect differential mortality. If mortality rates in the general population decrease over time at a faster rate than those for people with schizophrenia, then SMRs for people with schizophrenia will increase over time. The evidence from the current study suggests that this differential mortality gap has widened over time.

Mental health services have advanced in many parts of the world during the past few decades. Apart from a different mix of community-based care, the introduction of the second-generation antipsychotic medications in the early 1990s was initially found to be associated with better quality of life and reduced risk of relapse.[77-79] More recent trials have questioned the clinical superiority of second-generation antipsychotic medication,[80,81] and concern is now widespread about the adverse effects associated with these medications.[82] In particular, compared with typical antipsychotics, several of the second-generation antipsychotics are more likely to cause weight gain and metabolic syndrome.[83] Because the metabolic syndrome is associated with a 2-

Table 1. SMRs for Schizophrenia by Cause of Death for All Persons

Causes of Death	No. of SMRs	Quantile					Mean (SD)	Geometric Mean
		10%	25%	Median	75%	90%		
All-Cause and Middle-Level Categories								
All-cause (*ICD-9* codes 001-799/E800-E999)	38	1.18	1.87	2.58	3.64	5.76	2.98 (1.75)	2.68
All-natural cause (*ICD-9* codes 001-799)	6	0.99	1.04	2.41	2.90	4.10	2.31 (1.18)	2.03
All-unnatural cause (*ICD-9* codes E800-E999)	3	5.56	5.56	7.50	12.73	12.73	8.60 (3.71)	8.10
Natural Causes, Cause Specific								
Cardiovascular diseases (*ICD-9* codes 390-429)	7	1.11	1.40	1.79	2.49	3.60	2.01 (0.83)	1.88
Cerebrovascular diseases (*ICD-9* codes 430-438)	3	0.61	0.61	0.69	1.30	1.30	0.87 (0.38)	0.82
Digestive diseases (*ICD-9* codes 520-579)	5	1.79	2.24	2.38	2.50	17.50	5.28 (6.84)	3.34
Endocrine diseases (*ICD-9* codes 250-259)	3	2.20	2.20	2.63	11.66	11.66	5.50 (5.34)	4.07
Infectious diseases (*ICD-9* codes 001-139)	3	1.60	1.60	4.29	7.80	7.80	4.56 (3.11)	3.77
Genitourinary diseases (*ICD-9* codes 580-629)	3	1.54	1.54	3.70	4.29	4.29	3.18 (1.45)	2.90
Neoplastic diseases (*ICD-9* codes 140-239)	7	0.71	1.00	1.37	2.01	2.40	1.44 (0.60)	1.33
Nervous diseases (*ICD-9* codes 345-349)	4	1.60	1.95	4.22	6.57	7.00	4.26 (2.70)	3.55
Respiratory diseases (*ICD-9* codes 460-519)	6	2.20	2.39	3.19	3.80	9.30	4.01 (2.66)	3.51
Other diseases (*ICD-9* codes 1-389/630-799)	3	1.45	1.45	2.00	3.40	3.40	2.28 (1.01)	2.14
Unnatural Causes, Cause Specific								
Accident (*ICD-9* codes E800-E949)	6	1.20	1.63	1.73	5.10	8.40	3.30 (2.88)	2.51
Suicide (*ICD-9* codes E950-E959)	10	0.66	5.90	12.86	21.43	174.25	43.47 (95.11)	16.13

Abbreviations: ICD-9, *International Classification of Diseases, Ninth Revision (ICD-9)*; SMRs, standardized mortality ratios.

Table 2. SMRs for Schizophrenia of All-Cause Mortality by Economic Development Status for All Persons[a]

Economic Development Status	No. of SMRs	Quantile					Mean (SD)	Geometric Mean
		10%	25%	Median	75%	90%		
Least developed countries	4	1.88	1.89	2.02	2.75	3.36	2.32 (0.70)	2.25
Emerging economy countries	6	1.04	1.31	2.19	5.98	8.43	3.52 (3.03)	2.57
Developed countries	28	1.18	1.97	2.79	3.74	5.69	2.96 (1.52)	2.77

Abbreviation: SMRs, standardized mortality ratios.
[a] $F_{2,34} = 0.30$; $P = .74$.

to 3-fold increase in cardiovascular mortality and a 2-fold increase in all-cause mortality,[84] these adverse effects would be expected to contribute to even higher SMRs in the next few decades.[85,86] Unfortunately, we are unable to explore the role of atypical medications as a contributing factor for the increasing SMRs associated with schizophrenia (eg, deaths related to clozapine-induced agranulocytosis or deaths related to atypical antipsychotic-induced weight gain). Adverse health outcomes associated with weight gain and/or metabolic syndrome (eg, myocardial infarction, cerebrovascular accidents, or cancer) may take decades to fully emerge. Thus, it seems likely that studies undertaken in the 1990s (ie, the most recent studies included in this review) would capture only a small fraction of the eventual burden of mortality associated with the adverse effect profile of the second-generation antipsychotic medications. In light of the rising secular trends in SMRs already identified by this review, the prospect of further increases in mortality risks for schizophrenia is alarming.

In keeping with the findings of Harris and Barraclough[11] and Simpson,[10] we found no significant sex difference in all-cause SMRs. Thus, although many well-documented sex differences exist in the epidemiological features of schizophrenia,[19,87,88] the increased risk of mortality associated with schizophrenia affects men and women equally.

Of the specific-cause SMRs, suicide was associated with the highest estimate: 12 times greater than expected from the general population. In keeping with previous reviews, the SMRs associated with many different types of natural causes of death were elevated in people with schizophrenia. Curiously, the category neoplastic disorder had one of the lowest median SMRs (1.37). Although the median was still greater than 1, several record linkage studies[89] have suggested that cancers may be significantly less prevalent in people with schizophrenia. The current review examines only mortality, and studies that examine morbidity would be better able to explore this issue.[90]

We found no significant difference in SMRs among sites when sorted by economic status. However, this meta-analysis identified just 3 studies[53,58,61] that provided discrete SMRs from the least developed and emerging economy countries; thus, caution should be exercised in the interpretation of this finding. Furthermore, a single derived variable was used to define economic status, which was applied at the ecological level.

What factors have contributed to the differential mortality risk associated with schizophrenia? Many demo-

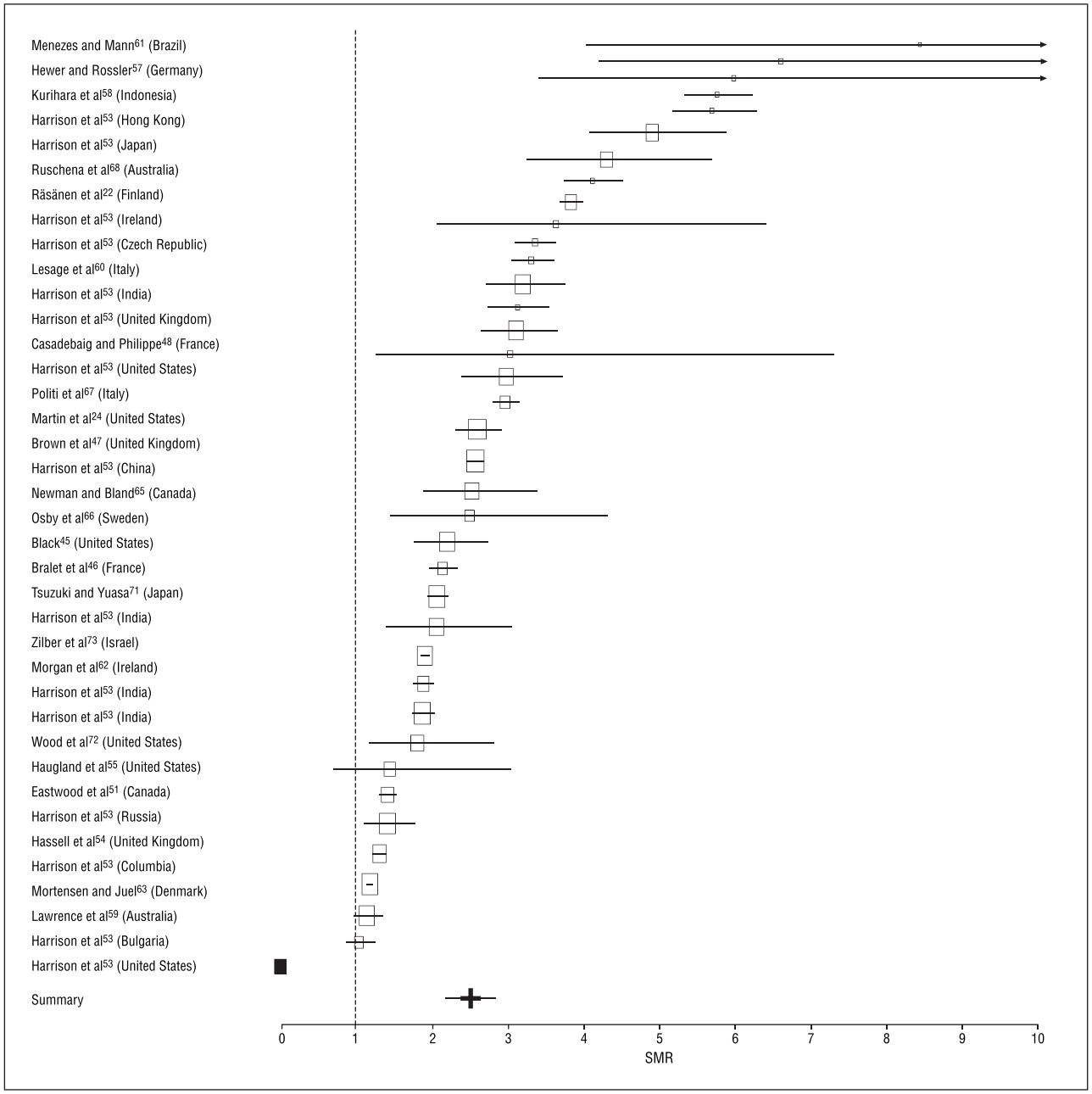

Figure 2. Forest plot of standardized mortality ratios (SMRs) for all-cause mortality in people with schizophrenia. Individual SMRs and the pooled estimate are shown with 95% confidence intervals (error bars). For each of the individual studies, the central open box symbol indicates the relative weighting on the pooled estimate (larger symbols indicate greater influence on the summary estimate). Standard errors cannot be calculated when the SMR is 0; thus, these values do not contribute to the pooled value. The upper 95% confidence limits for 3 studies extend beyond 10 (indicated with right arrow symbol). See also Supplementary Table S3 at www.qcmhr.uq.edu.au/epi.

graphic, clinical, political, and cultural factors mediate pathways and barriers to health care in general (eg, availability of services, stigma, and disease profiles).[91] With respect to schizophrenia, the onset of the illness can result in a cascade of unhealthy lifestyle factors that elevate the risk of various somatic diseases and consequently increase the risk of death. People with schizophrenia are thought to be less inclined to seek health care, to consume less medical care, to engage in high-risk behaviors, and to be less compliant with their treatments.[82,90,92] However, in addition to factors that operate on the pathway to care, schizophrenia and its associated comorbid somatic conditions may be downstream expressions of common genetic or environmental factors.[92,93] For example, it is feasible that polymorphisms in genes may increase the susceptibility to both schizophrenia and diabetes[94] or that de novo germline mutations across many generations could result in an increased risk of schizophrenia[95] and a wide range of adverse health outcomes. Prenatal nutritional disruptions may equally affect brain development and general metabolic functioning.[96,97] Although the current review cannot address these issues directly, the worsening SMRs associated with schizophrenia noted in recent decades

suggest that this already disadvantaged group is not benefiting from the improved health of the community in an equitable fashion. A systematic approach to monitoring and treating the physical health needs of people with schizophrenia is clearly warranted.[98]

Several important caveats to this review should be noted. Publication bias is always an issue in systematic reviews. We endeavored to address this by obtaining data from all available sources, including those from electronic databases, citations and authors, and publications in languages other than English. Factors such as the reliability of psychiatric diagnoses and admission practices (between sites and across time) could contribute to the variability identified in this systematic review. The reliability of the categorization of cause of death is also a cause for concern. With respect to specific-cause mortality, changes in the coding rules for the *ICD-9* and between-site variability in the application of these rules also need to be taken into account.[99,100] However, these issues do not affect all-cause SMRs (which were used for the main analyses in this review). The current study found a higher all-cause SMR (median SMR, 2.58; pooled meta-analysis SMR, 2.50) compared with the 2 previous reviews, which reported all-cause SMRs of 1.51[4] and 1.57.[11] The 2 previous systematic reviews were based on studies published before 1995[11] and 1996[4] compared with the current systematic review, which included 18 additional studies published after 1995.

In conclusion, compared with the general population, people with schizophrenia have a 2- to 3-fold increased risk of dying. Suicide contributes to the increased mortality associated with schizophrenia; however, people with schizophrenia have increased mortality risks attributable to a wide range of somatic conditions. The increased mortality risk affects both sexes equally. Substantial variation occurs in all-cause SMRs among sites. In recent decades, the differential mortality gap associated with schizophrenia has been increasing. It is sobering to reflect on this paradox of schizophrenia treatment. As we become better at detecting and treating the core symptoms of schizophrenia, patients have worsening SMRs. Given the potential for an even greater disease burden as a result of the introduction of second-generation antipsychotic medications, research aimed at optimizing the physical health of people with schizophrenia needs to be undertaken with a sense of urgency.

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Additional Information: The following additional material is available at www.qcmhr.uq.edu.au/epi: Figure S1: Flow Diagram (Selection Strategy) of Included Studies in the Mortality of Schizophrenia; Table S2: Quality Reporting Scale; Table S3: Summary Table of All-Cause Mortality and Standardized Mortality Ratio for Schizophrenia (1980-2006); Table S4: Standardized Mortality Ratios (SMRs) for Schizophrenia by Different Causes of Death for Males and Females; Table S5: Standardized Mortality Ratios for 3 Quality Score Tertiles of All-Cause Death; Table S6: Standardized Mortality Ratios for Schizophrenia of All-Cause Mortality for Various Post Hoc Analyses (for All Persons); and Microsoft Excel spreadsheet of the primary data for this systematic review, plus associated labels and formats.
Additional Contributions: Dozens of researchers from around the world assisted in locating the data for this systematic review, and the staff of the Queensland Centre for Mental Health Research assisted in extracting the data and preparing the original manuscript.

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EXHIBIT 23

Psychological Distress in Solitary Confinement: Symptoms, Severity, and Prevalence in the United States, 2017–2018

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Objectives. To specify symptoms and measure prevalence of psychological distress among incarcerated people in long-term solitary confinement.

Methods. We gathered data via semistructured, in-depth interviews; Brief Psychiatric Rating Scale (BPRS) assessments; and systematic reviews of medical and disciplinary files for 106 randomly selected people in solitary confinement in the Washington State Department of Corrections in 2017. We performed 1-year follow-up interviews and BPRS assessments with 80 of these incarcerated people, and we present the results of our qualitative content analysis and descriptive statistics.

Results. BPRS results showed clinically significant symptoms of depression, anxiety, or guilt among half of our research sample. Administrative data showed disproportionately high rates of serious mental illness and self-harming behavior compared with general prison populations. Interview content analysis revealed additional symptoms, including social isolation, loss of identity, and sensory hypersensitivity.

Conclusions. Our coordinated study of rating scale, interview, and administrative data illustrates the public health crisis of solitary confinement. Because 95% or more of all incarcerated people, including those who experienced solitary confinement, are eventually released, understanding disproportionate psychopathology matters for developing prevention policies and addressing the unique needs of people who have experienced solitary confinement, an extreme element of mass incarceration. (*Am J Public Health.* 2020;110:S56–S62. doi:10.2105/AJPH.2019.305375)

Long-term solitary confinement expanded across the United States in the 1980s; by 1997, nearly every state had built a "supermax," creating an estimated total of 20 000 new solitary cells.[1,2] Human rights agencies characterize the practice as torture[3,4]; policy analysts criticize it as expensive and ineffective.[2,4] Yet the epidemiological basis for understanding solitary confinement is weak. Current estimates of the annual US solitary confinement population vary from 80 000 to 250 000.[5,6] Likewise, the conditions (how much isolation with how few privileges), purposes (discipline, protection, or institutional security), and labels (administrative segregation, supermax, restrictive housing, intensive management) defining solitary confinement are contested.[2,5,6] Many studies document psychological harms of segregation, including associations between solitary confinement and self-harm, anxiety, depression, paranoia, and aggression, among other symptoms,[7–9] but other recent findings suggest that psychological impacts are limited.[10–12] Correctional officials use solitary confinement at their discretion, often with few procedural protections, limited available alternative responses, and no external oversight.[2] Researchers and policymakers are therefore limited not only in access to data and populations, but also by these populations' fluidity.

A standard instrument for assessing psychological impacts of incarceration is the Brief Psychiatric Rating Scale (BPRS). Originally developed to rate the severity of symptoms in hospitalized psychiatric patients and track changes in status over time,[13,14] the BPRS is increasingly used for research within carceral settings.[12,15,16,17] The current scale assesses 24 observable or self-reported symptoms. Extensive research on the BPRS's reliability and validity confirms its efficacy in identifying indicators of serious mental illness.[14]

In Washington State, interviewers administered the BPRS to a random sample of 87 incarcerated people during qualitative interviews (and also conducted 122 medical chart reviews),[1,9,15] concluding that solitary confinement reveals "a concentration of some of the most important negative effects of the entire prison complex."[1(p1692)] In a widely cited subsequent study, in Colorado, the BPRS was included in a battery of tests designed to measure psychological "constructs" associated with solitary confinement (for 270 matched participants), but generated

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few reliable results. The study relied on a pencil-and-paper test, the Brief Symptom Inventory, "a 53-item self-report measure . . . to assess a broad range of psychological symptoms," and concluded that people in solitary confinement sometimes experienced improvements in their psychological well-being, and those with mental illnesses did not deteriorate over time.[11(p52)]

Our study builds on these investigations, relying not only on psychometric instruments but also on mental and physical health and disciplinary records and in-depth interview data to assess the psychological well-being of 106 randomly sampled incarcerated people in long-term solitary confinement in the Washington State Department of Corrections (WADOC) from 2017 to 2018. Triangulation of sources gives this study a robust basis for understanding the psychological effects of solitary confinement.

METHODS

WADOC is a midsized (39th highest rate of incarceration in the United States), fully state-funded correctional system with a long history of inviting academic researchers to independently evaluate carceral practice.[1,9,18,19] Fieldwork was conducted over 2 separate 3-week periods in the summers of 2017 and 2018, by a total of 13 research team members (9 women and 4 men) all affiliated with the University of California, Irvine. In total, 106 incarcerated people were interviewed in 2017, and 80 incarcerated people were reinterviewed in 2018. We also collected medical and disciplinary data, including serious mental illness (SMI) and self-harm data.

Sample and Data Collections

WADOC has 5 geographically dispersed intensive management units (IMUs); people in these all-male units have usually violated an in-prison rule and are in solitary confinement for durations ranging from months to years, with highly restricted access to phones, radios, televisions, time out of cell, and visitors. As a result of WADOC efforts to reform and reduce IMU use, the population in these units fluctuated, with a high of more than 600 (in 2011) to a low of 286 incarcerated people (in 2015) on "maximum custody" status: for indeterminate terms, contingent on meeting specific benchmarks.[20] In 2017, when the initial sample for this research was drawn, there were 363 maximum custody status people assigned to the IMU.

We selected participants from a randomly ordered list in proportion to the population of each IMU, accounting for 29% of the total population in each of the 5 units. For recruitment and consent processes, see Appendix A (available as a supplement to the online version of this article at http://www.ajph.org). The interview refusal rate was 39% (67 out of 173 approached), comparable to similar studies of incarcerated people.[9,21]

The 96-question semistructured interview instrument included a range of questions used in previous studies on incarcerated people's experiences,[22,23] covering conditions of daily life, physical and mental health treatment, and IMU programming. BPRS self-report items were embedded throughout the interview; we evaluated observational items immediately following each interview.[24] Interviews lasted between 45 minutes and 3 hours.

Following interviews, participants were given an option to consent to medical file reviews and to participate in 1-year follow-up interviews. All participants consented to reinterviews, and all but 2 participants (n = 104) consented to medical file reviews. Following year-1 interviews, WADOC provided electronic administrative health and disciplinary files for all 104 consenting participants (along with comparable, population-level data for the prison system in 2017).

In summer 2018, the research team returned to Washington and reconsented and reinterviewed every available participant —notably including those no longer housed in the IMU—for a total of 80 reinterviews. Because of refusals (n = 4), institutional transfers and parole (n = 21), and 1 death, we were unable to follow-up with 26 respondents (25%). This drop-out rate is low compared with similar studies.[25,26] Follow-up interviews lasted between 45 minutes and 2 hours. The condensed year-2 instrument contained approximately 70 questions, with variation by current housing status.

For the steps taken to protect vulnerable imprisoned research participants and details of the training research team members completed, establishing high interrater reliability in administering the BPRS,[24] see Appendix A (available as a supplement to the online version of this article at http://www.ajph.org).

Data Analysis

All interviews were assigned a randomly generated identifier, digitally recorded, transcribed in Microsoft Word (Microsoft Corporation, Redmond, WA), translated (1 interview was conducted in Spanish), systematically stripped of identifying details (names, dates of birth), and entered into Atlas-ti (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) for analysis. See Appendix A for an explanation of the thematically grounded, open-coding process.[27] We entered all BPRS paper rating sheets, completed following year-1 and year-2 interviews, into Microsoft Excel (Microsoft Corporation, Redmond, WA). We linked each participant's BPRS rating, by random identifier, to extracted data from qualitative interviews, medical file reviews, and administrative data from WADOC.

Relevant variables extracted from administrative health data included SMI, a critical classification because it implies that treatment is medically necessary and, therefore, is an obligation of the prison system while the person is under its care. WADOC operationally defines SMI by standardized criteria combining diagnosis, medication, and frequency of psychiatric encounters, and history of suicide attempts or other self-harm.

We then imported BPRS and other administrative data into SPSS version 26 (IBM, Armonk, NY) to generate descriptive statistics, including prevalence of clinically significant ratings on BPRS items and factors (subscales of co-occurring symptom groups), including positive symptoms (unusual thought content, hallucinations, conceptual disorganization), negative symptoms (blunted affect, emotional withdrawal, motor retardation), depression-anxiety-guilt symptoms (including somatic concerns; DAGS), and mania (excitability, elevated mood, hyperactivity, distractibility).[14] We ran correlational analyses (cross-tabs and *t* test) to evaluate the relationships between BPRS ratings and other independent assessments of well-being, such as existing diagnosis of SMI.

RESULTS

See Table 1 for summary characteristics of the all-male participant population (there are no women in IMUs in WADOC) and the general WADOC population. As in other studies of solitarily confined incarcerated people,[6] our sample was generally younger, more violent (in terms of criminal history), and serving longer sentences than those in the general population. Latinos and gang affiliates are both overrepresented in our IMU sample, likely because of the salience of conflicts among rival Latino factions as an institutional security concern.[2] Although our IMU participants differed from the general prison population, there were no significant differences in either demographic variables or criminal history characteristics between our random sample and the overall IMU population, except that our participant pool was slightly older than the overall IMU population.

Range and Prevalence of Psychological Symptoms Identified

Our initial sample of 106 participants had a mean BPRS rating of 37 and a median rating of 33 (possible range from 24 to 168), suggesting mild psychiatric symptoms among the study population at the time of our interviews.[14] However, analysis of individual scale items showed clinically significant ratings (of 4 or higher of a possible 7) for as much as one quarter of the population sampled, especially for the depression and anxiety symptoms (Table 2). Further analysis of BPRS factors, as opposed to individual items, provided additional evidence of clinically significant psychiatric distress in as much as half of the population sampled (i.e., DAGS factor; Table 2).

Administrative data support the finding of long-term psychological distress. Among our respondents, 19% had SMI designations, 22% had a documented suicide attempt, and 18% had documentation of other self-harm, all at some point during their incarceration, either before or during their time in the IMU (Table 1). Moreover, respondents with SMI designations were much more likely to report positive symptoms and slightly more likely to report all other factored symptoms than non-SMI respondents (Table 3). These findings support the validity of the BPRS assessments.

TABLE 1—Characteristics of Sample of People in Solitary Confinement Compared With General Prison Population: Washington State Department of Corrections, 2017

	IMU Population (n = 106)	General Population (n = 16 465)[a]
Age, y		
Mean	35	40
Median	34	38
Range	20–65	18–94
Race/ethnicity, % (no.)		
White	42 (44)	59 (9746)
African American	12 (12)	18 (2935)
Latino	23 (24)	14 (2276)
Other	23 (24)	9 (1508)
IMU length of stay		
Mean	14.5 mo	. . .
Median	6 mo	. . .
Range	< 1 wk–151 mo	. . .
Current offense category, % (no.)		
Murder and manslaughter	17 (18)	16 (2623)
Sex offenses	12 (13)	19 (3195)
Robbery and assault	57 (60)	34 (5608)
Property offenses	8 (9)	18 (2933)
Drugs or other	6 (6)	13 (2106)
Prison convictions[b]		
Mean	5	4
Median	4	3
Range	1–18	1–27
Prison length of stay, mo		
Mean	103	97
Median	72	45
Range	3–456	2–600
Ever in prison gang,[c] % (no.)		
Yes	60 (64)	32 (5410)
No	36 (38)	68 (11 659)
Missing	4 (4)	. . .
Serious mental illness,[d] % (no.)	19 (16)	9 (1589)
Self-harm attempt,[e] % (no.)	18 (17)	Not available
Suicide attempt,[e] % (no.)	22 (22)	Not available

Note. IMU = intensive management unit.

[a]General population data excludes 761 nonsentenced and 718 resentenced incarcerated people. Both categories returned to prison for technical violations of conditions on underlying drug or sex offenses, a politically selective and narrow set of offenses that would distort the general population primary offense profile.

[b]Number of convictions to prison, excluding out-of-state convictions, often significant for IMU residents.

[c]Gang status was self-reported. Figure is calculated from 102 respondents who disclosed this information.

[d]Serious mental illness data were provided for 85 respondents; figure is calculated from this sample.

[e]Self-harm and suicide data were provided for 94 respondents; figure is calculated from this sample.

Qualitative interview data revealed symptoms not otherwise captured by the BPRS and medical files. (Such data will be used illustratively here, for reasons of space, and will be considered exhaustively in subsequent analyses). Two classes of symptoms were reported by a majority of respondents: descriptions of the severity of the emotional

TABLE 2—Brief Psychiatric Rating Scale Symptom and Factor Prevalence: Washington State Department of Corrections, 2017–2018

	IMU 2017 (n = 106), % (No.)	IMU 2018 (n = 28), % (No.)	Non-IMU 2018 (n = 52), % (No.)
Symptoms[a]			
Depression	24.50 (26)	25.00 (7)	15.38 (8)
Anxiety	24.50 (26)	32.14 (9)	28.85 (15)
Somatic concern	15.10 (16)	21.43 (6)	7.69 (4)
Guilt	17.90 (19)	17.86 (5)	7.69 (4)
Hostility	11.30 (12)	17.86 (5)	17.31 (9)
Hallucinations	9.40 (10)	14.29 (4)	11.54 (6)
Excitement	10.40 (11)	14.29 (4)	7.69 (4)
Factors[b]			
Positive	16.00 (17)	17.86 (5)	11.54 (6)
Negative	4.70 (5)	0 (0)	1.92 (1)
DAGS	49.10 (52)	53.57 (15)	36.54 (19)
Mania	17.00 (18)	14.81 (4)	17.31 (9)

Note. DAGS = depression, anxiety, guilt, and somatization; IMU = intensive management unit; mania = elevated mood, distractibility, motor hyperactivity, and excitement; negative = blunted affect, emotional withdrawal, and motor retardation; positive = hallucinations, unusual thought content, and conceptual disorganization.

[a]Only clinically significant symptoms (rating of 4 or higher) that were reported by 10% or more of the sample are presented.

[b]Factors combine 3 or 4 different symptoms that are commonly associated with one another.[14]

toll of being in the IMU (80% of respondents; cumulatively, the topic was mentioned 359 times) and feelings of social isolation (73% of respondents; cumulatively, the topic was mentioned 192 times). This interview excerpt exemplifies the "emotional toll" descriptions:

> I bet you couldn't walk in my shoes because all the stuff you got to endure behind these walls of pain. There's a lot you got to go through . . . [and] I've been doing this for 11 years . . . people adapt to their surroundings, but to get used to this life, I don't [think] you can. (Michael, a pseudonym, as with all subsequent quotations)

And this quotation exemplifies social isolation:

> You're not around people. I'm around somebody right now with handcuffs and shackles on like I'm an animal. It's dehumanizing. No human contact. As [a] human being, I feel like we're meant to socialize, and it does have an effect on your mentality while you're sitting in the cell. (Chase)

Two additional symptoms were as prevalent as other clinically significant BPRS items like anxiety: references to sensory hypersensitivity (16% of respondents mentioned this at least once) and loss of identity (25% of respondents mentioned this at least once). Respondents discussed hypersensitivity to sounds, smells, "[and . . .] tiny things" (Giovanni). In particular, the sounds of doors opening and closing aggravated many respondents:

> All you got to do is hold it. I mean, you don't got to slam it. It's like [correctional officers] showing their power. . . . That ain't cool. You wouldn't do that in your house, would you? (Tyler).

Respondents also talked about the institution taking over their identity:

> I've been in the hole so long that it defines the person. If you've been in the box for so long, you can't play well with others. . . . We're so confined in that box. It's like a safety blanket. (Eli).

Another respondent echoed a frequent complaint about the lack of mirrors contributing to the loss of identity:

> This IMU has mirrors in the cell. The majority of them do not. And it gets really stressful when you can't even see your own reflection. . . . I mean when you can't even look at yourself, you lose some of your self-identity. (Eric)

Comparing Symptoms in and out of Solitary Confinement (2018)

Of the 80 respondents reinterviewed in the second year of this study, 28 were in IMU custody and 52 were in the general prison population. These 2 subpopulations provide important comparison groups between IMU residents and people in the general population, because all initially entered the study through a random sample of IMU residents. These subpopulations also provide a longitudinal view of how incarcerated people experience IMU conditions over 1 year and how they recover from these conditions as they re-enter the general population. In Table 2, we compare, cumulatively by subpopulation, symptom and factor scores in 2017 for IMU residents to 2018 scores for IMU respondents and respondents not in the IMU. For respondents still in the IMU in 2018, all clinically significant symptoms that were prevalent among at least 10% of the population were at least as prevalent in 2018, and 2 clinically significant factor scores were more prevalent (positive, DAGS). For respondents

TABLE 3—Serious Mental Illness Status and 2017 Brief Psychiatric Rating Scale Factor Prevalence: Washington State Department of Corrections, 2017–2018

	SMI (n = 16), % (No.)	Non-SMI (n = 69), % (No.)
Positive	50 (8)	10.14 (7)
Negative	6.30 (1)	4.40 (3)
DAGS	56.30 (9)	47.80 (33)
Mania	18.75 (3)	13 (9)
Population[a]	18.80 (16)	81.20 (69)

Note. DAGS = depression, anxiety, guilt, and somatization; mania = elevated mood, distractibility, motor hyperactivity, and excitement; negative = blunted affect, emotional withdrawal, and motor retardation; positive = hallucinations, unusual thought content, and conceptual disorganization; SMI = serious mental illness.

[a]Mental health data were available only for 85 of 106 sampled incarcerated people.

not in the IMU in 2018, the prevalence of clinically significant symptoms varied from more prevalent than in the 2017 sample (e.g., anxiety) to less prevalent (e.g., somatic concerns and guilt), and factor scores were either lower (i.e., positive, negative, DAGS) or similar (for mania) for respondents not in the IMU in 2018. Despite having an exceptionally large sample size for a study of a solitary confinement population, our study was not powered to establish statistically significant differences between the 2017 and 2018 data sets.

DISCUSSION

In this study, we combined qualitative interview data with structured, quantitative measures of psychological and psychiatric outcomes in solitary confinement among 106 randomly sampled incarcerated people in Washington State, documenting both a wide range and high prevalence of symptoms of psychological distress. We highlight 4 major implications of this.

First, while the overall BPRS ratings we analyzed indicated limited psychological distress, as documented in earlier studies,[11,12] a closer examination of specific items and factors revealed that as many as half of respondents had at least 1 clinically significant symptom within the BPRS anxiety–depression factor. Because other studies using the BPRS in solitary confinement settings employed earlier 18-item versions of the scale,[15] used the scale in combination with other scales,[11] or analyzed only total ratings,[12] our findings are not directly comparable with those in other BPRS studies. However, our findings are consistent with other studies, including findings that 20% or more of Washington incarcerated people in solitary exhibited a "marked or severe degree of distress,"[15(p774)] and that more than half of California incarcerated people in solitary reported "symptoms of psychological distress."[28(p133)] Our findings therefore highlight the importance of analyzing specific components of BPRS scores, and not only aggregates, which mask variation in both prevalence and severity of specific symptoms.

Second, administrative data confirmed that our participants had relatively high rates of documented mental health problems, including rates of SMI and self-harming behavior (Table 1). SMI rates, typically estimated at 10% to 15% of prison populations,[8,29] are measured at 9% in Washington's general prison population but 20% in our IMU sample. Likewise, our qualitative data confirmed that people in solitary confinement experience symptoms specific to those conditions not captured in standard psychiatric assessment instruments.[30] Both findings suggest an affirmative answer to the question of whether solitary confinement is associated with more and worse psychopathology than general population confinement. As longitudinal case studies have illustrated,[9,30] disproportionate representation of incarcerated people with psychopathology in solitary confinement reflects the interaction of clinical and security factors in prison custody decisions: solitary confinement responds to behavior expressing psychopathology, often undiagnosed, and also aggravates the propensity of some incarcerated people to break down or act out.[31] For these reasons, the causal role of solitary confinement is not established by aggregate comparisons of IMU and non-IMU populations.

Third, the comparisons we were able to make across multiple sources of data allowed us to identify a broader range of symptoms of distress than studies that have focused on only 1 or 2 sources of data, such as administrative data,[8] psychiatric assessments,[11] or qualitative interviews.[28,30] Symptoms such as anxiety and depression were especially prevalent in this population, along with symptoms ostensibly specific to solitary confinement, such as sensory hypersensitivity and a perceived loss of identity (as found in other studies exploring solitary-specific symptoms[7,9,15,28,30,32]).

Finally, consistent with previous studies,[11,12] we found that the prevalence of psychiatric distress did not significantly increase over time for incarcerated people that either stay or are released from the IMU 1 year later. Yet our qualitative data suggest that the BPRS may not be capturing actual psychopathology, as respondents pointed to psychiatric distress—in profoundly existential terms, as in the previously mentioned quotations regarding selfhood and identity—beyond the 2-week time period evaluated by the BPRS and outside the scope of the instrument. Moreover, although symptoms were not cumulatively found to worsen, they did persist at high rates, for incarcerated people in and out of the IMU, in 1-year follow-up assessments. These latter findings are also consistent with other studies, underscoring the need for additional research comparing incarcerated people's experiences across different contexts and over time.[1,7,15,28,32]

Limitations

Five specific limitations are especially notable. First, although our initial sample was relatively large for a solitary confinement population, our 1-year follow-up group, especially the number of respondents remaining in solitary confinement in the second year, was relatively small, limiting our ability to establish statistically significant findings about change over time and across contexts from BPRS data. Second, as our interview results revealed, the BPRS does not capture the full spectrum of psychiatric distress incarcerated people experience in solitary confinement. Third, assessments of psychological well-being would ideally occur at multiple times, beyond the 2 we were able to conduct within the constraints of this multimethod study. Fourth, Washington State is not representative of most state prison systems in terms of the prevalence of people with mental illnesses in solitary confinement, as WADOC has undertaken reforms in both treatment of mental illness and imposition of solitary confinement over the past 20 years, including reforms designed to divert people with serious mental illness to specialized treatment units.[33] Moreover, these reforms have radically improved systematic mental health record-keeping; we would expect not only a lower prevalence of psychiatric symptoms and less deterioration in WADOC in IMUs but also a higher rate of documentation of those symptoms that are present. Finally, although people in solitary confinement may exhibit distinctive or disproportionately severe psychopathology, causal inference regarding the relationship between solitary confinement and psychopathology is beyond the analysis we are able to perform here.

Conclusions and Implications

We found a wide range and high prevalence of symptoms of psychiatric distress in this population, including BPRS symptoms associated with anxiety and depression among

as many as half of our participants, administrative indicators of SMI among at least one fifth of our participants, and condition-specific symptoms, such as feelings of extreme social isolation, in well more than half of our participants. Moreover, these symptoms persisted in the second year for participants in and out of solitary confinement.

If we study people in solitary confinement solely with instruments validated with non-incarcerated populations, such as the BPRS, we may fail to capture the extent of incarcerated people's psychological distress. A respondent's rating on a given symptom may not be "high enough"; symptoms may not be experienced within the instrument's designated time frame; or the discursive strategies incarcerated people use to articulate their suffering might not correspond with clinical language. Moreover, past research reveals that incarcerated people develop coping mechanisms for solitary,[1,2,32] and these, along with the fact that speaking openly about psychological distress conflicts with institutional norms of self-protection in prison,[1,2,30] likely contribute to a systematic underreporting of distress. These are critical limitations of standardized assessments of incarcerated people whose symptoms may fluctuate substantially in presence and severity during time in solitary.[1,7,32] Apart from symptoms or their severity, this fluctuation, itself, is an integral aspect of incarcerated people's psychological distress,[34] but a need for repeated measurement makes it especially difficult to capture.

Our findings still point to the importance of using standardized instruments, which provide a baseline for assessing and interpreting the psychological effects of solitary confinement. Nonetheless, additional sources of evidence—interviews, clinician observations, staff observations, medical files—are crucial for capturing the range of symptoms that people in solitary exhibit, and those symptoms' prevalence, duration, and severity over time. Without the benefit of mixed methods and improved instruments, researchers and policymakers alike will continue not only to lack desired data but also to not know what data we lack. Increasing the transparency of both conditions of confinement and the associated health effects is critical to both question formulation and data gathering.

As 5% to 15% of the United States' 1.6 million incarcerated people are held in solitary confinement for at least part of their incarceration,[5,6] and virtually all of those people will be released, all members of society have a vested interest in limiting the induction of psychopathology suggested by findings such as those presented here. At least some of the symptoms we described here, including identity loss and hypersensitivity, resulted directly from specific conditions of confinement, such as the absence of mirrors and the repetitive slamming of doors. To the extent that solitary is meant to make people more manageable, its association with psychopathology calls into question its usefulness, let alone its justice. And to the extent that solitary confinement has any causative role in psychopathology, our collective goal should be prevention. AJPH

CONTRIBUTORS

K. Reiter served as principal investigator on this study, led data collection and analysis, and conceptualized and led the writing of this article. J. Ventura trained the study team in applying the Brief Psychiatric Rating Scale (BPRS), consulted on data collection and analysis, and participated in writing this article. D. Lovell consulted on study design and data collection, led the analysis of administrative data, and participated in writing this article. D. Augustine, M. Barragan, K. Chesnut, P. Dashtgard, G. Gonzalez, N. Pifer, and J. Strong participated in project design, participant interviews, data analysis, and writing of this article. K. Chesnut also served as project manager and, with P. Dashtgard, participated in administrative data and BPRS analysis. T. Blair consulted on data analysis and participated in writing this article.

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Note. The views expressed here are those of the authors and do not necessarily represent those of the Washington DOC or other data file contributors. Any errors are attributable to the authors.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

HUMAN PARTICIPANT PROTECTION

This study was approved by the institutional review board at the University of California, Irvine (HS 2016-2816).

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EXHIBIT 24

Solitary Confinement and Mental Illness in U.S. Prisons: A Challenge for Medical Ethics

Jeffrey L. Metzner, MD, and Jamie Fellner, Esq.

In recent years, prison officials have increasingly turned to solitary confinement as a way to manage difficult or dangerous prisoners. Many of the prisoners subjected to isolation, which can extend for years, have serious mental illness, and the conditions of solitary confinement can exacerbate their symptoms or provoke recurrence. Prison rules for isolated prisoners, however, greatly restrict the nature and quantity of mental health services that they can receive. In this article, we describe the use of isolation (called segregation by prison officials) to confine prisoners with serious mental illness, the psychological consequences of such confinement, and the response of U.S. courts and human rights experts. We then address the challenges and human rights responsibilities of physicians confronting this prison practice. We conclude by urging professional organizations to adopt formal positions against the prolonged isolation of prisoners with serious mental illness.

J Am Acad Psychiatry Law 38:104–8, 2010

Physicians who work in U.S. prison facilities face ethically difficult challenges arising from substandard working conditions, dual loyalties to patients and employers, and the tension between reasonable medical practices and the prison rules and culture. In recent years, physicians have increasingly confronted a new challenge: the prolonged solitary confinement of prisoners with serious mental illness, a corrections practice that has become prevalent despite the psychological harm it can cause. There has been scant professional or academic attention to the unique ethics-related quandary of physicians and other healthcare professionals when prisons isolate inmates with mental illness. We hope to begin to fill this gap.

Solitary confinement is recognized as difficult to withstand; indeed, psychological stressors such as isolation can be as clinically distressing as physical torture.[1,2] Nevertheless, U.S. prison officials have increasingly embraced a variant of solitary confinement to punish and control difficult or dangerous prisoners. Whether in the so-called supermax prisons that have proliferated over the past two decades or in segregation (i.e., locked-down housing) units within regular prisons, tens of thousands of prisoners spend years locked up 23 to 24 hours a day in small cells that frequently have solid steel doors. They live with extensive surveillance and security controls, the absence of ordinary social interaction, abnormal environmental stimuli, often only three to five hours a week of recreation alone in caged enclosures, and little, if any, educational, vocational, or other purposeful activities (i.e., programs). They are handcuffed and frequently shackled every time they leave their cells.[3–5] The terms segregation, solitary confinement, and isolation will be used interchangeably to describe these conditions of confinement.

Isolation can be psychologically harmful to any prisoner, with the nature and severity of the impact depending on the individual, the duration, and particular conditions (e.g., access to natural light, books, or radio). Psychological effects can include anxiety, depression, anger, cognitive disturbances, perceptual distortions, obsessive thoughts, paranoia, and psychosis.[6]

The adverse effects of solitary confinement are especially significant for persons with serious mental illness, commonly defined as a major mental disorder (e.g., schizophrenia, bipolar disorder, major depressive disorder) that is usually characterized by psy-

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Disclosures of financial or other potential conflicts of interest: None.

chotic symptoms and/or significant functional impairments. The stress, lack of meaningful social contact, and unstructured days can exacerbate symptoms of illness or provoke recurrence.[7] Suicides occur disproportionately more often in segregation units than elsewhere in prison.[8–10] All too frequently, mentally ill prisoners decompensate in isolation, requiring crisis care or psychiatric hospitalization. Many simply will not get better as long as they are isolated.

Mental health professionals are often unable to mitigate fully the harm associated with isolation. Mental health services in segregation units are typically limited to psychotropic medication, a health care clinician stopping at the cell front to ask how the prisoner is doing (i.e., mental health rounds), and occasional meetings in private with a clinician.[7] Individual therapy; group therapy; structured educational, recreational, or life-skill-enhancing activities; and other therapeutic interventions are usually not available because of insufficient resources and rules requiring prisoners to remain in their cells.[11]

The use of segregation to confine the mentally ill has grown as the number and proportion of prisoners with mental illness have grown. Although designed and operated as places of punishment, prisons have nonetheless become *de facto* psychiatric facilities despite often lacking the needed mental health services.[7] Studies and clinical experience consistently indicate that 8 to 19 percent of prisoners have psychiatric disorders that result in significant functional disabilities, and another 15 to 20 percent require some form of psychiatric intervention during their incarceration.[12] Sixty percent of state correctional systems responding to a survey on inmate mental health reported that 15 percent or more of their inmate population had a diagnosed mental illness.[13]

Despite significant improvements in correctional mental health services, often related to litigation and development of standards and guidelines by the National Commission on Correctional Health Care (NCCHC), the American Psychiatric Association (APA), and other professional organizations, in many prisons the services remain woefully inadequate. Relative to the number of prisoners needing help, there is an insufficient number of qualified staff, too few specialized facilities, and few programs.[7] Mindful of budget constraints and scant public support for investments in the treatment (as opposed to punishment) of prisoners, elected officials have been reluctant to provide the funds and leadership needed to ensure that prisons have sufficient mental health resources. Twenty-two of 40 state correctional systems reported in a survey that they did not have an adequate mental health staff.[13]

Persons with mental illness are often impaired in their ability to handle the stresses of incarceration and to conform to a highly regimented routine. They may exhibit bizarre, annoying, or dangerous behavior and have higher rates of disciplinary infractions than other prisoners. Prison officials generally respond to them as they do to other prisoners who break the rules. When lesser sanctions do not curb the behavior, they isolate the prisoners in the segregation units, despite the likely negative mental health impact. Once in segregation, continued misconduct, often connected to mental illness, can keep the inmates there indefinitely.[7,14]

In class action cases challenging the segregation of inmates with serious mental illness as unconstitutionally cruel because of the psychological harm it can inflict, U.S. federal courts have either issued rulings or accepted settlements that prohibit or sharply curtail the practice. According to one federal judge, putting mentally ill prisoners in isolated confinement "is the mental equivalent of putting an asthmatic in a place with little air. . . ."[15] Unfortunately, except in the small number of prisons governed by the outcome of such litigation, mentally ill prisoners continue to be sent to segregation; indeed, they are often disproportionately represented in segregation units.[16,17]

International treaty bodies and human rights experts, including the Human Rights Committee,[18] the Committee against Torture,[19,20] and the U.N. Special Rapporteur on Torture,[21] have concluded that solitary confinement may amount to cruel, inhuman, or degrading treatment in violation of the International Covenant on Civil and Political Rights[22] and the Convention against Torture and other Cruel, Inhuman, and Degrading Treatment or Punishment.[23] They have specifically criticized supermax confinement in the United States because of the mental suffering it inflicts.[19,20] Whatever one's views on supermax confinement in general, human rights experts agree that its use for inmates with serious mental illness violates their human rights.

Principles of ethics regarding beneficence, nonmaleficence, and respect for the rights and dignity of all patients have led international and national profes-

sional organizations to affirm that physicians are ethically obligated to refrain from countenancing, condoning, participating in, or facilitating torture or other forms of cruel, inhuman, or degrading treatment.[24–27] Involvement of healthcare practitioners in abusive interrogations recently prompted the American Medical Association[28] and the APA[29] to oppose the participation of physicians in interrogations. Two years ago, the NCCHC issued a position statement that correctional health care professionals "should not condone or participate in cruel, inhumane or degrading treatment of inmates."[30] To date, however, the medical organizations have not formally acknowledged that prolonged isolation of the mentally ill constitutes cruel or inhuman treatment in violation of human rights, nor have they addressed health professionals' ethics-related responsibilities when faced with such cases.

Correctional health care professionals struggle with constrained resources and large caseloads that limit the services they can provide their patients. It is ethical for them to do the best they can under the circumstances rather than resigning, which would result in even fewer services for their patients. But what are practitioners' ethics-related responsibilities when prison officials impose conditions of confinement that exacerbate the symptoms of a prisoner's mental illness?

The ethic-based calculus physicians face when prisoners are isolated for disciplinary or security reasons is different than that created by the struggle with limited resources. Segregation of mentally ill prisoners (or any other prisoner) is not an unintended consequence of tight budgets, for example. It reflects a penal philosophy and the conscious decision by prison officials about whom to isolate, for how long, and under what conditions. If health professionals simply do their rounds but say nothing, are they implicitly legitimizing the segregation of mentally ill prisoners and thereby contributing to the continuation of the harm? What must they do to avoid being complicit in conditions of confinement that may well constitute a human rights violation?

We believe it is ethical for physicians to treat prisoners who have been abused, but they must also take measures to end the abuse. In addition to providing whatever services they can to segregated patients, they should advocate within the prison system for changed segregation policies and, if that fails, they should undertake public advocacy.[31–33]

Publically exposing and urging change in harmful prison practices is difficult and, needless to say, can threaten job security, but individual practitioners should not have to wrestle alone with a prison practice that violates human rights norms. Their professional organizations should help them. Through the organizations, health professionals collectively can support colleagues who work in prisons in the quest to ensure ethically defensible correctional policies. The APA[34] and the NCCHC[35] have provided basic frameworks for increased mental health monitoring and treatment of segregated inmates. They must do more, however.

Professional healthcare organizations should acknowledge that prolonged segregation of inmates with serious mental illness violates basic tenets of mental health treatment. The mental health standards of the NCCHC include the "optional recommendation" that mentally ill prisoners be excluded from extreme isolation,[35] noting in an appendix that clinicians "generally agree that placement of inmates with serious mental illnesses in settings with 'extreme isolation' is contraindicated because many of these inmates' psychiatric conditions will clinically deteriorate or not improve (Working Group on Schizophrenia, 1997)."[36,37] In light of that general consensus, shouldn't the NCCHC make the exclusion mandatory, instead of optional? The APA and AMA should also formally adopt a similar position.

However, adopting a similar position is easier said than done. Very few physicians in the APA and AMA have experience or knowledge regarding correctional mental health care, let alone correctional environments in general. They are not familiar with the differences between a general population housing unit and a disciplinary segregation housing unit. Administrative segregation, supermax, rules infractions, mental health rounds, and "kites" are terms most noncorrectional physicians do not understand. In short, we recognize that a serious educational effort must be mounted so that noncorrectional mental health practitioners have a better understanding of the world in which their correctional colleagues work and the unique challenges they face, including the isolation of seriously ill patients for months, even years, that would never be condoned in a noncorrectional mental health setting.

No doubt some correctional mental health clinicians will not agree with us. They may believe the isolation of volatile mentally ill prisoners is necessary

for security reasons. They may believe they are guests in the house of corrections who have no business addressing custody policies, or they may have become so accustomed to the extended use of isolation that they have lost sight of its potential to cause psychological harm.

Experience demonstrates that prisons can operate safely and securely without putting inmates with mental illness in typical conditions of segregation. Because of litigation, in some prisons, mentally ill prisoners who would otherwise be locked in their cell for 23 to 24 hours a day are given more time outside their cells, including time in group therapy and other therapeutic interventions.[11] The improved clinical responses of prisoners with mental illness have been achieved without sacrificing needed controls or relinquishing the goal of holding those accountable, whether mentally ill or not, who willfully violate prison rules.

The professional organizations should acknowledge that it is not ethically defensible for health care professionals to acquiesce silently to conditions of confinement that inflict mental harm and violate human rights. They should affirm that practitioners are ethically obligated, not only to treat segregated inmates with mental illness, but also to strive to change harmful segregation policies and practices.[31–33] Finally, the organizations should not be content with clarifying the ethics-related responsibilities of individual practitioners in these circumstances. They should actively support practitioners who work for changed segregation policies, and they should use their institutional authority to press for a nationwide rethinking of the use of isolation. The medical professions' commitment to ethics and human rights would be well served by such steps.

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EXHIBIT 25

No. 15-31

IN THE

Supreme Court of the United States

ALFREDO PRIETO,

Petitioner,

v.

HAROLD C. CLARKE, ET AL.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Fourth Circuit

BRIEF OF *AMICI CURIAE* PROFESSORS AND PRACTITIONERS OF PSYCHIATRY AND PSYCHOLOGY IN SUPPORT OF PETITIONER

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TABLE OF CONTENTS

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF AUTHORITIES

Page(s)

TABLE OF AUTHORITIES
(continued)

Page(s)

TABLE OF AUTHORITIES
(continued)

Page(s)

TABLE OF AUTHORITIES
(continued)

Page(s)

INTEREST OF THE *AMICI CURIAE*[1]

Amici curiae are professors and practitioners of psychiatry and psychology with extensive experience studying the psychological effects of imprisonment, including solitary confinement.

Carl Fulwiler, M.D., Ph.D., is a board-certified psychiatrist and neuroscientist, and currently is Assistant Professor of Psychiatry at the University of Massachusetts Medical School and Tufts University School of Medicine. Dr. Fulwiler's research focuses on violent behavior by the mentally ill. As a practitioner, he specializes in the diagnosis and treatment of mental illness among inmates and former inmates, and has interviewed over two hundred inmates in over a dozen segregation units.

Craig Haney, Ph.D., J.D., is Professor of Psychology at the University of California, Santa Cruz. He has been studying prison conditions for more than 30 years, and has inspected numerous prisons, including multiple supermax facilities, in the United States. Dr. Haney has evaluated approximately 1,000 isolated prisoners, and has written extensively about the psychological effects of solitary confinement.

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[1] Counsel of record received timely notice of the intention to file this brief, and all parties have consented to the filing of this brief. As required by Rule 37.6, *amici* state that no counsel for a party authored this brief in whole or in part, and no person other than *amici*, their members, and their counsel made any monetary contribution intended to fund the preparation or submission of this brief.

Terry A. Kupers, M.D., is Institute Professor at the Wright Institute and practices psychiatry in California. He provides expert testimony as well as consultation and staff training regarding the psychological effects of prison conditions, including solitary confinement. He is the author of Prison Madness: The Mental Health Crisis Behind Bars and What We Must Do About It (1999).

Pablo Stewart, M.D., is a board-certified psychiatrist who is currently a Clinical Professor of Psychiatry at the UCSF School of Medicine. He has over 30 years experience working in the criminal justice system, including 10 years as a federal-court-appointed psychiatric expert on the effects of solitary confinement on inmates' mental health. He also served as a consultant to the New Mexico Department of Corrections concerning the mental health of prisoners in solitary confinement. In addition to his academic duties, Dr. Stewart works as a forensic psychiatric consultant for various governmental and private agencies.[2]

Hans Toch, Ph.D., is Distinguished Professor Emeritus in the School of Criminal Justice at the State University of New York at Albany. He has written numerous texts considered "classics" about

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[2] In September 2007, Dr. Stewart examined Mr. Prieto in his role as an expert witness for Mr. Prieto in *Prieto v. Ayers*, No. 2:05-cv-7566 (C.D. Cal.). Dr. Stewart also testified on behalf of Mr. Prieto in *Commonwealth v. Prieto*, No. FE05-1764 (Va. Cir. Ct. Fairfax Cnty.). *See Prieto v. Zook*, __ F.3d __, 2015 WL 3960915, at *5 (4th Cir. June 30, 2015) (describing Dr. Stewart's testimony). Other than as an *amicus curiae* in this Court, Dr. Stewart has had no role or involvement in this case.

the psychology of imprisonment and hundreds of articles on prison-related topics, and has served as a consultant to several correctional systems. He also has received multiple awards for distinguished contributions to criminology and penology.

Amici's decades-long dedication to studying the unique psychological harms of solitary confinement and to urging reform of its conditions and use gives *amici* a strong interest in the resolution of the question presented here. *Amici* seek to highlight for the Court the scientific literature that concludes virtually unanimously that solitary confinement can cause significant psychological harm to all prisoners forced to endure its conditions. *Amici* also explain that the psychological harms of solitary confinement are far greater than those created by ordinary incarceration, presenting a significant risk of harm unique to solitary-confinement inmates.

SUMMARY OF THE ARGUMENT

I. The relevant scientific research firmly establishes that prolonged solitary confinement causes severe psychological harms by imposing social isolation and sensory deprivation.

A. Solitary confinement is the practice of confining inmates to cells generally no larger than 80 square feet for between 22 and 24 hours a day. The defining features of solitary confinement are twofold: social isolation and reduced environmental stimuli. Prisoners have virtually no opportunity for meaningful social contact or productive activities.

B. Social isolation and sensory deprivation cause severe psychological harm. Psychological research outside of the prison context establishes the

necessity of social contact and environmental stimuli for human wellbeing, and that denial of social and environmental stimuli can result in severe psychological distress, including hallucinations, anxiety, panic, impaired memory, and psychotic behavior.

C. Studies of inmates in solitary confinement overwhelmingly establish that prolonged solitary confinement causes adverse psychological effects.

Inmates in solitary confinement suffer from a wide range of adverse symptoms, including panic, cognitive dysfunction, hallucinations, paranoia, depression, emotional breakdowns, self-mutilation, and suicidal impulses. Although the symptoms are wide-ranging, their manifestation is "strikingly consistent" among inmates. Indeed, studies from different decades, by researchers from varying academic backgrounds, and in different countries have "reached remarkably consistent conclusions about the adverse psychological consequences of solitary confinement." And in light of this research, experts have identified a distinct "isolation" syndrome associated with prolonged solitary confinement.

Beyond the specific psychological harms associated with isolation syndrome, prisoners develop "social pathologies" that cause permanent changes in their personality.

Moreover, *all* prisoners in long-term solitary confinement are at risk of psychological harm. Even psychologically resilient individuals with no history of mental illness suffer psychological harm in the extreme conditions of solitary confinement. In

addition to causing psychological harm de novo, solitary confinement exacerbates existing mental illness, placing mentally ill inmates at a greater risk of experiencing the specific psychological harms associated with isolation syndrome.

II. Solitary confinement imposes far greater harm than ordinary incarceration. Prisoners in solitary confinement suffer mental illness at approximately twice the rate of prisoners in the general population, and fully half of all prison suicides occur in solitary confinement, even though solitary-confinement prisoners comprise less than 10 percent of the prison population. These higher rates of mental illness and psychiatric symptoms, moreover, cannot be attributed solely to pre-existing mental illness in inmates sent to solitary confinement—studies instead point to the damaging psychological effects of solitary confinement *itself*. Studies comparing isolated and non-isolated prisoners further demonstrate the increased psychological effects of solitary confinement relative to ordinary imprisonment, and confirm the causal link between solitary confinement and psychological harm.

The severe psychological harms imposed by solitary confinement render it a different kind of imprisonment entirely, and amount to an "atypical and significant hardship" within the meaning of *Wilkinson v. Austin*, 545 U.S. 209, 223 (2005).

ARGUMENT

I. THE PHYSICAL AND SOCIAL ISOLATION OF PROLONGED SOLITARY CONFINEMENT IMPOSES SEVERE PSYCHOLOGICAL HARM.

By depriving prisoners of social interaction and environmental stimuli critical to mental health, prolonged solitary confinement causes significant and well documented psychological effects. The literature "is virtually unanimous in its conclusion: prolonged supermax solitary confinement can and does lead to significant psychological harm." Thomas L. Hafemeister & Jeff George, *The Ninth Circle of Hell: An Eighth Amendment Analysis of Imposing Prolonged Supermax Solitary Confinement on Inmates with a Mental Illness*, 90 Denv. U. L. Rev. 1, 35 (2012). The psychological effects of solitary confinement are wide ranging, yet strikingly consistent among inmates across various studies, countries, and centuries. And while mentally ill prisoners are particularly susceptible to these harms, solitary confinement affects even psychologically resilient individuals—prolonged periods of solitary confinement "manufacture or increase mental illness," Gary C. Mohr & Rick Raemisch, *Restrictive Housing: Taking the Lead*, Corrections Today (2015), *available at* http://www.aca.org/ACA_PROD_IMIS/Docs/Corrections%20Today/2015%20Articles/March%202015/Guest%20Editorial.pdf. Accordingly, all inmates in solitary confinement are at significant risk of severe psychological harm.

A. Solitary Confinement Imposes Social Isolation and Restricts Environmental Stimuli.

Solitary confinement here refers to the involuntary placement of a prisoner alone in a cell separated from the mainstream prison population, generally as a form of punishment, for an average of 22-24 hours each day with minimal opportunity for social interaction or meaningful activity.[3] *See* Stuart Grassian, *Psychiatric Effects of Solitary Confinement*, 22 Wash. U. J.L. & Pol'y 325, 327 (2006); Craig Haney & Mona Lynch, *Regulating Prisons of the Future: A Psychological Analysis of Supermax and Solitary Confinement*, 23 N.Y.U. Rev. L. & Soc. Change 477, 496 (1997).

Solitary confinement is generally considered "prolonged" when it exceeds three months, Terry A. Kupers, *Isolated Confinement: Effective Method for Behavior Change or Punishment for Punishment's Sake?*, *in* The Routledge Handbook for Int'l Crime & Just. Studies 213, 214 (Bruce A. Arrigo & Heather Y. Bersot eds., 2014), though the United Nations has concluded "that 15 days is the limit between 'solitary confinement' and 'prolonged solitary confinement' because at that point" psychological effects "can become irreversible," U.N. Special Rapporteur, Interim Report of the Special Rapporteur on Torture

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[3] Prison administrators refer to solitary-confinement units using various labels, including supermax prisons, "Special Housing Units," "Special Management Units," and "administrative segregation." *See* Elizabeth Bennion, *Banning the Bing: Why Extreme Solitary Confinement Is Cruel and Far Too Usual Punishment*, 90 Ind. L.J. 741, 746 (2015).

and Other Cruel, Inhuman or Degrading Treatment or Punishment, at 9, U.N. Doc. A/66/268 (Aug. 5, 2011). In any event, United States prisoners on average live for years, not months, in solitary confinement. For example, in the federal supermax prison, inmates subjected to solitary confinement spend an average of 8.2 years in such confinement. Amnesty International, *Entombed: Isolation in the US Federal Prison System* 20 (July 2014), *available at* http://www.amnestyusa.org/sites/default/files/amr510402014en.pdf; *see also* Solitary Watch, FAQ, http://solitarywatch.com/facts/faq (compiling average solitary-confinement periods for various states).

Solitary confinement socially isolates prisoners and deprives them of environmental stimuli. Prisoners live in windowless (or nearly windowless) cells measuring between 60 and 80 square feet that contain a bunk, toilet, and sink. Reassessing Solitary Confinement: The Human Rights, Fiscal, and Public Safety Consequences: Hearing Before the Subcomm. on the Constitution, Civil Rights & Human Rights of the S. Comm. on the Judiciary, 112th Cong. 75 (2012) (prepared statement of Dr. Craig Haney) (hereinafter "Solitary Hearing"). Prisoners spend virtually all of their time in these cells, forcing them to "sleep, eat, and defecate … in spaces that are no more than a few feet apart from one another." *Id.* When prisoners do leave their cells, it is to exercise either in a metal cage or in an enclosed concrete pen, *id.* at 77, "areas that are so constraining they are often referred to as 'dog runs,'" Craig Haney, *Mental Health Issues in Long-Term Solitary and "Supermax" Confinement*, 49 Crime &

Delinquency 124, 126 (2003). Prisoners thus live constantly in "barren 'industrial' environments," "surrounded by nothing but concrete, steel, cinderblock, and metal fencing." Solitary Hearing at 76.

Further isolating prisoners, they have no opportunity for normal physical contact with others. Virtually all solitary-confinement units prohibit contact visits. *Id.* As a result, prisoners' only physical contact often is with correctional officers who place them in restraints. Hafemeister, 90 Denv. U. L. Rev. at 17. Prisoners in solitary confinement can be imprisoned for years without touching another person with affection. Solitary Hearing at 76.

In addition to physically isolating prisoners, solitary confinement socially isolates them. Prisoners have "no opportunity for normal conversation or association with others." Elizabeth Bennion, *Banning the Bing: Why Extreme Solitary Confinement Is Cruel and Far Too Usual Punishment*, 90 Ind. L.J. 741, 743 (2015). Even interactions between prisoners and staff are minimal, as cameras, intercoms, and computerized locking and tracking systems permit staff to monitor prisoners without interacting with them. Haney, *Mental Health Issues* at 126. Thus, "socially and psychologically meaningful contact is reduced to a minimum." Peter Scharff Smith, *The Effects of Solitary Confinement on Prison Inmates: A Brief History and Review of the Literature*, 34 Crime & Just. 441, 449 (2006).

Solitary confinement also forces prisoners to endure extreme idleness. Inmates generally have no

access to rehabilitative, education, or work programs. Bennion, 90 Ind. L.J. at 753; *see also* Kupers, *Isolated Confinement* at 213 ("Few if any rehabilitation programs exist in supermaxes."). They have "literally nothing meaningful to do." Solitary Hearing at 77.

This describes Petitioner's confinement. Petitioner spends 23 hours or more each day alone in a 71-square-foot cell. And because each cell has solid metal doors (which prevent communication between inmates, Grassian, 22 Wash. U. J.L. & Pol'y at 346), Petitioner "is deprived of almost all human contact, even cell-to-cell contact with other death row inmates," App.21a-22a. He has no opportunity to participate in education or work programs, and his out-of-cell exercise time takes place in a metal cage approximately the same size as his cell. *Id.* at 30a.

B. Social Isolation And Sensory Deprivation Have Severe Psychological Consequences.

Psychological research on isolation and sensory deprivation outside of the prison context establishes that social contact and environmental stimuli are critical to maintaining mental health.

Studies on sensory deprivation—interfering with the stimulation a person normally receives from his environment—well illustrate the importance of sensory and perceptual stimuli. Haney, 23 N.Y.U. Rev. L. & Soc. Change at 500. Placement in an "unchanging monotonous environment" "deprives the sensory organs of normal levels of stimulation." Bennion, 90 Ind. L.J. at 759. The brain processes that deprivation as stress, resulting in elevated

cortisol levels that produce anxiety, paranoia, and interference with memory. *Id.* More extreme sensory deprivation can cause "perceptual distortions, hallucinatory experiences, and sometimes high levels of anxiety." Haney, 23 N.Y.U. Rev. L. & Soc. Change at 500. For example, air force pilots flying alone at high altitudes, where auditory and visual stimulation is limited, have reported severe anxiety and detachment from reality, including hallucinations. Bennion, 90 Ind. L.J. at 760.

Social isolation likewise has well-established adverse effects. Social contact is essential "for the creation and maintenance of 'self.'" Haney, 23 N.Y.U. Rev. L. & Soc. Change at 503. Interacting with others is how humans interpret emotions. *Id.* Without social interaction, unrealistic thoughts "cannot be tested in conversation with others, so they build up inside and are transformed into unfocused and irrational thoughts." Kupers, *Isolated Confinement* at 215.

Unsurprisingly, then, social isolation and psychiatric illness are connected. Individuals who are "unmarried, unemployed, living alone, or without religious affiliations" tend to seek out mental-health services more frequently than socially connected individuals. Haney, 23 N.Y.U. Rev. L. & Soc. Change at 505. And isolated individuals can "suffer from symptoms that resemble posttraumatic stress disorder—including 'anxiety, nervousness, ... depression, difficulty sleeping, inability to work, and difficulty trusting people, as well as difficulties adapting to the world outside of confinement.'" Bennion, 90 Ind. L.J. at 760.

Several factors entailed in prolonged solitary confinement, moreover, can intensify these harmful psychological effects. "Experimental research has demonstrated that an individual who ... experience[s] the isolation situation as potentially threatening is far more likely to develop adverse psychiatric reactions." Grassian, 22 Wash. U. J.L. & Pol'y at 347. At California's Pelican Bay State Prison, for example, psychological-distress rates of solitary-confinement prisoners were on average 14.5 percent higher than for protective-custody prisoners—prisoners who were similarly isolated but for a protective rather than punitive purpose. Haney, *Mental Health Issues* at 137. The psychological effects also vary with the perceived duration of confinement. In particular, the "more indeterminate" the period of deprivation is, the greater the damaging effects. Amnesty International, *Entombed* 31; *see also* Haney, 23 N.Y.U. Rev. L. & Soc. Change at 501 ("[I]nforming subjects of the upper time limit of the study enhanced their ability to tolerate the isolation.").

In short, imposing social isolation and sensory deprivation has "drastic" effects on people. Indeed, that solitary confinement, involving stimulus deprivation and a near-total loss of control, "is among the most frequently used psychological torture techniques seems to underscore its aversive nature and destructive potential." Haney, 23 N.Y.U. Rev. L. & Soc. Change at 506.

C. Prolonged Solitary Confinement Causes Strikingly Similar Psychological Harms In A Substantial Percentage Of Prisoners.

These conclusions about social isolation and sensory deprivation are strongly confirmed by studies specific to solitary confinement, which "consistently and unequivocally" establish that solitary confinement causes adverse psychological effects. Haney, *Mental Health Issues* at 130. While the symptoms are wide-ranging, their manifestation is both remarkably consistent and highly prevalent among inmates in solitary confinement—prisoners in solitary confinement develop an "isolation" syndrome. These consistent and widespread psychological effects establish that *all* prisoners in prolonged solitary confinement are at risk of psychological deterioration.

1. Research on solitary confinement reports a wide array of psychological harms.

Prisoners in solitary confinement suffer various negative psychological effects, ranging from anxiety and panic to self-mutilation and suicide to changes in brain function. Haney, 23 N.Y.U. Rev. L. & Soc. Change at 530.

Among other psychological effects, inmates become hypersensitive to external stimuli, such as smells and noises. *Id.* For example, a prisoner reported that he "became enraged by routine noises—the sound of doors opening as the guards made their hourly checks, the sounds of inmates in nearby cells." Atul Gawande, *Hellhole*, The New

Yorker, Mar. 30, 2009, http://www.newyorker.com/magazine/2009/03/30/hellhole. Noises also might take on increased significance. An inmate in one study noted that noises "start[ed] to sound like sticks beating men." Stuart Grassian, *Psychopathological Effects of Solitary Confinement*, 140 Am. J. Psychiatry 1450, 1452 (1983).

Hallucinations and other perceptual distortions also affect inmates. Haney, 23 N.Y.U. Rev. L. & Soc. Change at 530. Prisoners have "hallucinated that the colors on the walls were changing," Gawande, *Hellhole*, http://www.newyorker.com/magazine/2009/03/30/hellhole, and have reported "wavering cell walls, movements, and even the experience of entire visits in the cell," Smith, 34 Crime & Just. at 491. Inmates in solitary confinement also have "described hearing voices, often in whispers and often saying frightening things to them." Grassian, 22 Wash. U. J.L. & Pol'y at 335.

Prisoners additionally have difficulty with concentration, thinking, and memory. Grassian, *Psychopathological Effects* at 1453. They also experience lethargy and chronic tiredness. Smith, 34 Crime & Just. at 492. Such effects are symptoms of changes that occur in the brain as a result of the extreme idleness imposed by solitary confinement. In an experimental study of sensory deprivation in a Canadian maximum-security prison, socially isolated inmates exhibited slowed EEG, "which 'correlated with apathetic, lethargic behavior.'" *Id.*; *see also* Grassian, 22 Wash. U. J.L. & Pol'y at 331 ("[E]ven a few days of solitary confinement will predictably

shift the electroencephalogram (EEG) pattern toward an abnormal pattern characteristic of stupor and delirium.").

Impulse control also suffers while prisoners remain in solitary confinement. Haney, 23 N.Y.U. Rev. L. & Soc. Change at 530. As one prisoner related, "I snap off the handle over absolutely nothing. Have torn up mail and pictures, throw things around." Grassian, 22 Wash. U. J.L. & Pol'y at 336.

Studies also report self-destructive behavior. Prisoners "become so desperate and despondent that they engage in self-mutilation." Solitary Hearing at 80. Terry Anderson, an Associated Press reporter held hostage for seven years, "snapped" after three years in solitary confinement, and beat his head against a wall until he was bleeding. Bennion, 90 Ind. L. J. at 753-54. A "prisoner in New Mexico ... used a makeshift needle and thread from his pillowcase to sew his mouth completely shut." Solitary Hearing at 80-81. Another "amputated one of his pinkie fingers and chewed off the other, removed one of his testicles and scrotum, sliced off his ear lobes, and severed his Achilles tendon with a sharp piece of metal." *Id.* Individuals in solitary confinement also report suicidal impulses, and "a disturbingly high number" of inmates in solitary confinement resort to suicide. *Id.* at 80. While less than 10 percent of prisoners live in solitary confinement, half of prison suicides occur there. *Id.* at 79; *see* Bennion, 90 Ind. L.J. at 757.

In sum, prisoners in solitary confinement experience "a wide range of harmful psychological effects, including increases in negative attitudes and

affect, insomnia, anxiety, panic, withdrawal, hypersensitivity, ruminations, cognitive dysfunction, hallucinations, loss of control, aggression, rage, paranoia, hopelessness, lethargy, depression, emotional breakdowns, self-mutilation, and suicidal impulses." Haney, 23 N.Y.U. Rev. L. & Soc. Change at 530.

Those who have experienced both extreme physical pain and solitary confinement describe isolation as being "as torturous and agonizing as any physical abuse they suffered." Bennion, 90 Ind. L.J. at 753. Senator John McCain, for example, has said that solitary confinement "crushes your spirit and weakens your resistance more effectively than any other mistreatment," and he "was beaten regularly; denied adequate medical treatment for two broken arms, a broken leg, and chronic dysentery; and tortured to the point of having an arm broken again." *Id.*

2. The strikingly consistent and prevalent psychological effects of solitary confinement indicate that it causes a distinct psychological syndrome.

These wide-ranging effects of solitary confinement are both consistent and highly prevalent.

Nearly all the symptoms documented in solitary-confinement studies are "strikingly consistent" among inmates. Grassian, *Psychopathological Effects* at 1452. Indeed, the scientific literature "has reached remarkably similar conclusions about the adverse psychological consequences of solitary

confinement." Solitary Hearing at 81; *see also* Haney, *Mental Health Issues* at 130-31 (citing for each adverse symptom numerous studies reporting that symptom); Hafemeister, 90 Denv. U. L. Rev. at 36 (discussing a variety of studies on solitary confinement, and noting that they "have consistently reported the same adverse symptoms"); Smith, 34 Crime & Just. at 507-18 (collecting more than 25 separate studies documenting similar adverse effects); Haney, 23 N.Y.U. Rev. L. & Soc. Change at 496-503, 511-29 (discussing empirical research, descriptive accounts, and case studies on the psychological effects of solitary confinement).

These modern studies also are consistent with observations of solitary-confinement prisoners in the nineteenth century, when the United States and European countries experimented with solitary confinement as a method of rehabilitating prisoners. Smith, 34 Crime & Just. at 457. Germany in particular developed "a psychiatric literature on 'prison psychoses.'" *Id.* at 466. That literature "described a hallucinatory, paranoid, confusional psychosis in which characteristic symptoms included … extremely vivid hallucinations" affecting all of the senses, "aimless violence," and persecutory delusions, symptoms also observed in modern-day studies. Grassian, *Psychopathological Effects* at 1451.

Moreover, these psychological symptoms are highly prevalent—a substantial percentage of prisoners suffer from them. Solitary Hearing at 82. Specifically, "[r]esearch suggests that between one-third and more than 90 percent experience adverse symptoms in solitary confinement." Smith, 34 Crime

& Just. at 502. For example, in Dr. Grassian's 1983 in-depth study of 14 prisoners in Walpole, Massachusetts, 11 were hypersensitive to external stimuli. Half of the prisoners suffered from hallucinations or illusions. And 8 of the 14 prisoners suffered difficulties with thinking, concentration, and memory. Three prisoners reported cutting themselves in suicide attempts. Grassian, *Psychopathological Effects* at 1453.

Dr. Haney, in a study of 100 randomly selected inmates in solitary confinement in Pelican Bay likewise "found extraordinarily high rates of symptoms of psychological trauma." Reassessing Solitary Confinement: The Human Rights, Fiscal, and Public Safety Consequences: Hearing Before the Subcomm. on the Constitution, Civil Rights & Human Rights of the S. Comm. on the Judiciary, 112th Cong. 496 (2012) (comments by Dr. Terry Kupers). "[V]irtually all" prisoners—91%—experienced nervousness and anxiety and 70% "felt themselves on the verge of an emotional breakdown." Haney, *Mental Health Issues* at 133. Moreover, "[a]lmost all … prisoners reported suffering from ruminations or intrusive thoughts, an oversensitivity to external stimuli, irrational anger and irritability, confused thought processes, difficulties with attention and often with memory, and a tendency to withdraw socially." *Id.* at 134 (reporting that over 80% of prisoners suffered these symptoms). Hallucinations and other perceptual distortions affected 41% of prisoners, and 27% had thoughts of suicide. *Id.*

Other studies similarly report high rates of psychological effects. In a study of mentally ill prisoners in solitary confinement, 53% had attempted suicide at least once. Correctional Association of New York, *Mental Health in the House of Corrections: A Study of Mental Health Care in New York State Prisons* 57 (2004), *available at* http://www.correctionalassociation.org/wp-content/uploads/2004/06/Mental-Health.pdf. Moreover, 40% reported self-mutilation, *id.* at 59, and 70% had difficulty thinking, concentrating, or paying attention, *id.* at 55.

Given the consistency and prevalence of symptoms experienced by prisoners in solitary confinement, experts have classified these symptoms as a distinct "syndrome, calling it 'isolation sickness,' 'reduced environmental stimulation syndrome,' or 'security housing unit syndrome.'" Hafemeister, 90 Denv. U. L. Rev. at 30; *see also* Haney, 23 N.Y.U. Rev. L. & Soc. Change at 518 (describing Dr. Hans Toch's finding "that 'isolation panic' was a serious problem" in solitary confinement). As Dr. Grassian has explained, the symptoms observed in solitary confinement "are almost pathogonomic of the syndrome, meaning they are symptoms virtually found nowhere else." Grassian, 22 Wash. U. J.L. & Pol'y at 337. "[T]he fact that all of these quite unusual symptoms ran together … was itself a clear confirmation of the distinct nature of this syndrome." *Id.* at 338.

3. Solitary confinement has additional disabling effects.

Beyond the measurable psychological harms of isolation syndrome, solitary confinement affects

prisoners' patterns of thinking and acting. These "social pathologies," while not "clinical syndromes per se," are "equally if not more problematic" for inmates' health. Haney, *Mental Health Issues* at 138. The patterns that prisoners develop in adapting to solitary confinement often are permanent. *See* Solitary Hearing at 83.

For example, after adapting to solitary confinement's environment of total control, prisoners no longer can set limits for themselves, and "become uncomfortable with even small amounts of freedom." Haney, *Mental Health Issues* at 139. Some inmates might "lose the ability to initiate behavior of any kind." *Id.*

Additionally, the nearly total deprivation of social contact creates the risk that prisoners will "los[e] their grasp on who they are." *Id.* While in solitary confinement, prisoners become desperate for any human response, even a negative one. They might attempt to trigger an emergency "cell extraction"—a "brutal" removal from their cell—simply "to reaffirm their existence." Solitary Hearing at 77. Prisoners' desperation also explains "the high prevalence of feces, urine, and semen throwing that occurs universally" in solitary confinement. Hafemeister, 90 Denv. U. L. Rev. at 37. Although these actions make their living conditions even worse, prisoners act out to "prov[e] to themselves that they are still alive and capable of eliciting a genuine response—however hostile—from other human beings." Haney, *Mental Health Issues* at 139-40. That same lack of social contact can cause other prisoners to severely withdraw to the point that they become frightened by social contact. *Id.* at

140. Indeed, "[e]ven the prospect of returning to the comparative 'freedoms' of a mainline maximum security prison … fills them with anxiety." Solitary Hearing at 83.

The recent story of Kalief Browder illustrates these harms. After three years in prison waiting for a trial date, including 17 months in solitary confinement, "[e]verybody could see that he had changed." Jennifer Gonnerman, *Before The Law*, The New Yorker, Oct. 6, 2014, http://www.newyorker.com/magazine/2014/10/06/before-the-law. Kalief recognized it, too: "I'm mentally scarred right now … [T]here are certain things that changed about me and they might not go back." *Id.* Six months after his release, he tried to slit his wrists and, when a friend stopped him, he tried to hang himself from a banister. *Id.* A year later, he had deteriorated further, throwing out his television because, he said, "it was watching me." Jennifer Gonnerman, *Kalief Browder, 1993-2015*, The New Yorker, June 7, 2015, http://www.newyorker.com/news/news-desk/kalief-browder-1993-2015. This past June, two years after he had been released, he committed suicide by hanging himself with an air-conditioning cord from a bedroom window. *Id.*

4. Solitary confinement is potentially harmful to all prisoners.

The high rates of similar adverse psychological effects in solitary-confinement prisoners establish that solitary confinement creates a risk of harm to *all* prisoners. Solitary Hearing at 81. Indeed, solitary confinement is so "toxic to mental functioning" that "even those inmate[s] who are more

psychologically resilient inevitably suffer severe psychological pain," Grassian, 22 Wash. U. J.L. & Pol'y at 354, and may become mentally ill, Bennion, 90 Ind. L.J. at 743. For example, highly educated women with "a history of relatively strong psychological functioning" nonetheless "demonstrated significant psychopathological reactions to their prolonged confinement," including anxiety, panic attacks, and perceptual disturbances. Grassian, 22 Wash. U. J.L. & Pol'y at 352-53. Similarly, a prisoner in California with no pre-existing mental illness became "catatonic, unresponsive, and incoherent" in isolation. Solitary Hearing at 87.

Inmates with mental illness are particularly vulnerable to the psychological effects of isolation. Hafemeister, 90 Denv. U. L. Rev. at 38. "The stress, lack of meaningful social contact, and unstructured days can exacerbate symptoms of illness or provoke recurrence." Jeffrey L. Metzner & Jamie Fellner, *Solitary Confinement and Mental Illness in U.S. Prisons: A Challenge for Medical Ethics*, 38 J. Am. Acad. Psychiatry & L. 104, 105 (2010). And "[a]ll too frequently, mentally ill prisoners decompensate in isolation, requiring crisis care or psychiatric hospitalization." *Id.* This particularly harmful impact on the mentally ill is significant, because approximately one-third of solitary-confinement inmates are mentally ill. Solitary Hearing at 78-79. Mentally ill prisoners often lack the capacity to follow the rigid rules and procedures of prison life, and so are more likely to end up in solitary confinement as punishment for rule violations. Haney, *Mental Health Issues* at 142; *see also*

Hafemeister, 90 Denv. U. L. Rev. at 49 ("prison officials often 'treat disordered behavior as disorderly behavior.'").

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In sum, "[t]he empirical record compels an unmistakable conclusion"—solitary confinement "is psychologically painful, can be traumatic and harmful, and puts many of those who have been subjected to it at risk of long-term emotional and even physical damage." Haney, 23 N.Y.U. Rev. L. & Soc. Change at 500. Accordingly, "the overall conclusion must be that solitary confinement—regardless of specific conditions and regardless of time and place—causes serious health problems for a significant number of inmates." Smith, 34 Crime & Just. at 502-03.

II. SOLITARY CONFINEMENT IMPOSES FAR GREATER PSYCHOLOGICAL HARM THAN ORDINARY IMPRISONMENT.

In light of this Court's focus on whether conditions amount to "atypical and significant hardship," *Wilkinson*, 545 U.S. at 223, it is important to recognize that the conditions of solitary confinement create a far greater risk of psychological harm for prisoners than do the conditions of ordinary incarceration. Both the overall rates of mental illness in solitary confinement compared to the general population, and studies comparing isolated and non-isolated prisoners, provide convincing support for the increased harm of solitary confinement.

A. Prisoners In Solitary Confinement Have Higher Rates Of Mental Illness Than General-Population Prisoners.

The higher rates of mental illness in solitary-confinement prisoners reflect the "significant additional strain and additional health problems" caused by solitary confinement. Smith, 34 Crime & Just. at 503. Solitary confinement imposes social isolation and sensory deprivation to a much greater extent than ordinary imprisonment. Haney, 23 N.Y.U. Rev. & Soc. Change at 497. Predictably, then, "[s]olitary confinement produces a higher rate of psychiatric and psychological health problems than 'normal' imprisonment." Smith, 34 Crime & Just. at 476. Experts estimate that prisoners in solitary confinement suffer from mental illness at twice the rate of the general prison population. Hafemeister, 90 Denv. U. L. Rev. at 46; Haney, *Mental Health Issues* at 142. Approximately one-third of prisoners in solitary confinement suffer from mental illness. Solitary Hearing at 78-79. By contrast, in the general prison population, approximately 15% of inmates are mentally ill. Treatment Advocacy Center & National Sheriffs' Association, *More Mentally Ill Persons Are in Jails and Prisons Than Hospitals: A Survey of the States* at 1 (May 2010), *available at* http://www.treatmentadvocacycenter.org/storage/documents/final_jails_v_hospitals_study.pdf.

Prisoners in solitary confinement also engage in higher rates of self-destructive behavior than general-population prisoners. For example, in a study of North Carolina and Virginia prisons, more than half of all self-mutilation incidents occurred in

solitary-confinement units. Haney, 23 N.Y.U. Rev. L. & Soc. Change at 525. And a study last year found that solitary-confinement prisoners were nearly seven times more likely to harm themselves than prisoners in the general population. *See* Homer Venters et al., *Solitary Confinement and Risk of Self-Harm Among Jail Inmates*, 104 Am. J. Pub. Health 442, 442-47 (2014). Suicide rates, too, are disproportionately high in solitary confinement. Indeed, "[o]ne of the most stunning and inescapable statistical facts" regarding solitary confinement is that half of prison suicides occur among the 2-8% of prisoners in solitary confinement. Stuart Grassian & Terry Kupers, *The Colorado Study vs. The Reality of Supermax Confinement*, Correctional Mental Health Rep. 1 (May/June 2011).

These higher rates of mental illness and psychiatric symptoms cannot be attributed solely to the fact that mentally ill prisoners are more likely to end up in solitary confinement. Solitary-confinement prisoners themselves "consistently identify punitive segregation as the source of their psychic trauma." Haney, 23 N.Y.U. Rev. L. & Soc. Change at 533. Moreover, the consistent and highly prevalent psychological effects reported among solitary-confinement prisoners substantially "undercut the possibility that nothing more than pre-existing dysfunction is being manifested." *Id.* These effects instead "point to the damaging psychological effects of punitive, isolated prison housing *itself*." *Id.* at 529 (emphasis added).

B. Studies Confirm That Solitary Confinement Causes Greater Harm To Prisoners Than Ordinary Incarceration.

Studies involving isolated prisoners and a control group of non-isolated prisoners are "especially convincing[]" in demonstrating the increased harm of solitary confinement relative to ordinary imprisonment. Smith, 34 Crime & Just. at 476. For example, in a study of 34 Kentucky inmates, solitary-confinement prisoners "reported more feelings of inadequacy, inferiority, withdrawal, and isolation," as well as "rage, anger, and aggression," than the general prison population. *Id.* at 455. Similarly, a Danish study involving 367 prisoners found nearly twice as many prisoners in solitary confinement compared to the general population experienced psychiatric problems. *Id.* at 477. The Danish study also concluded that a prisoner in solitary confinement was 20 times more likely to be hospitalized for a psychiatric reason than a prisoner in the general population. *Id.*

A study of 30 solitary-confinement prisoners and 28 general-population prisoners reported a similar divergence in psychological effects. "The group of isolated inmates 'showed considerably more psychopathological symptoms than the control group.'" *Id.* at 476. The authors also concluded that the divergence was "'mainly caused by solitary confinement; age, schooling, duration of detention and personality turned out to be of subordinate importance.'" *Id.* at 476-77.

Craig Haney's study of 25 maximum-security prisoners and 41 randomly selected solitary-confinement prisoners at Pelican Bay in 2013

likewise revealed significant differences in the prevalence of psychological symptoms. Erica Goode, *Solitary Confinement: Punished for Life*, N.Y. Times, Aug. 3, 2015, http://www.nytimes.com/2015/08/04/health/solitary-confinement-mental-illness.html?_r=1. "While 63 percent of the men in solitary for more than 10 years said they felt close to an 'impending breakdown,' only 4 percent of the maximum-security inmates reported feeling that way." *Id.* Similarly, seventy-three percent of solitary-confinement inmates reported chronic depression, compared with 48% of maximum-security inmates. *Id.*

Data from a recent study in Colorado also indicate that solitary confinement imposes unique harms beyond those experienced by general-population prisoners. The 59 mentally ill inmates in solitary confinement experienced a total of 37 incidents—an average of 0.62 incidents per inmate—of either suicidal behavior, self-destructive behavior, or emergence of psychotic symptoms. Grassian & Kupers, *Colorado Study* at 7-8. By contrast, during the same period the 33 inmates with mental illness in the general population experienced only three such incidents, or 0.09 incidents per inmate. *Id.* Thus, psychiatric crises "were dramatically more prevalent" among mentally ill prisoners in solitary confinement compared with mentally ill inmates housed in the general population. *Id.* at 9.

Accordingly, prolonged solitary confinement causes far greater psychological harm than ordinary incarceration, posing an atypical and severe risk of harm to inmates who must endure its conditions. The relevant scientific literature unequivocally

establishes the severe and wide-ranging psychological harms of solitary confinement. That "research … confirms what this Court suggested over a century ago: Years on end of near-total isolation exact a terrible price." *Davis v. Ayala*, 135 S. Ct. 2187, 2210 (2015) (Kennedy, J., concurring). This case thus presents an important issue warranting the Court's review.

CONCLUSION

The petition for a writ of certiorari should be granted.

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Respectfully submitted,

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EXHIBIT 26

Craig Haney

The Psychological Effects of Solitary Confinement: A Systematic Critique

ABSTRACT

Research findings on the psychological effects of solitary confinement have been strikingly consistent since the early nineteenth century. Studies have identified a wide range of frequently occurring adverse psychological reactions that commonly affect prisoners in isolation units. The prevalence of psychological distress is extremely high. Nonetheless, use of solitary confinement in the United States vastly increased in recent decades. Advocates defend its use, often citing two recent studies to support claims that isolation has no significant adverse psychological effects, including even on mentally ill people. Those studies, however, are fundamentally flawed, their results are not credible, and they should be disregarded. Critically and comprehensively analyzing the numerous flaws that compromise this recent scholarship underscores the distinction between methodological form and substance, the danger of privileging quantitative data irrespective of their quality, and the importance of considering the fraught nature of the prison context in which research results are actually generated. Solitary confinement has well-documented adverse effects. Its use should be eliminated entirely for some groups of prisoners and greatly reduced for others.

Doing prison research, Alison Liebling has long reminded us, is deeply emotional and intellectually challenging, with different methodological approaches "competing for epistemological prominence—often from different sides of the prison wall" (1999, p. 148). It takes place in "an in-

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tense, risk-laden, emotionally fraught environment" (p. 163) and within a closed environment in which prison administrators tightly control access to data and most prisoners manifest an entirely legitimate and understandable skepticism toward data gatherers.

This helps explain why, in Liebling's words, "the pains of imprisonment are tragically underestimated by conventional methodological approaches to prison life" (p. 165). The more these conventional approaches encourage us to conceive of prisons as more or less traditional research settings and prisoners as mere specimens to be "objectively assessed," the less likely we are to gain useful insights into prison life or accurately represent the experience of those living inside.

These cautions are doubly applicable to research on solitary confinement.[1] It involves involuntary isolation of prisoners nearly around the clock in sparse cells located in remote or inaccessible units. Solitary confinement denies prisoners any meaningful social contact and access to positive environmental stimulation.

These prisons within prisons are nearly impenetrable to outside researchers (or anyone else). Prison officials tightly control access to solitary confinement units and to the prisoners inside them. They typically rebuff attempts by researchers to observe conditions and practices, let alone to carefully assess their potentially harmful effects. Prisoners in solitary confinement tend to be even more self-protective than other prisoners are (as part of their accommodation to harsh and frequently abusive conditions) and reluctant to have their "measure" taken by persons whom they have no reason to trust. They generally subscribe strongly to prisoner norms against displaying or acknowledging vulnerabilities that could be interpreted as weakness. The inapt pejorative designation of them as collectively "the worst of the worst" does not inspire confidence in or candor toward outsiders, and certainly not toward anyone remotely associated with the prison administration.

These realities pose a host of methodological challenges for anyone interested in understanding the nature and effects of prison isolation. This is in part why studies of the effects of solitary confinement on prisoners

[1] I use "solitary confinement" to refer to forms of prison isolation in which prisoners are housed involuntarily in their cells for upward of 23 hours per day and denied the opportunity to engage in normal and meaningful social interaction and congregate activities, including correctional programming. The term subsumes a range of prison nomenclature including "administrative segregation," "security housing units," "high security," and "close management," among others.

have rarely, if ever, approximated experimental research designs (including quasi- or natural experimental designs).

Solitary confinement units not only are largely impenetrable to outsiders but also, of course, are subject to legal and ethical restrictions that preclude random assignment of prisoners into them. The rigid prison rules and operating procedures that govern these places can easily frustrate the use of the kind of meticulous controls over conditions and participants that are needed to carry out anything remotely resembling an experiment. The distinctiveness of solitary confinement units and the nonnegotiable staff mandates under which they operate make it difficult, if not impossible, to implement rigorous conventional research designs (e.g., representative samples, control groups, repeated measures). Efforts to conduct randomized or truly controlled studies inevitably face significant risks that the data collected will be so confounded by inevitable methodological compromises as to be uninterpretable and, therefore, meaningless.

Nonetheless, scholars and researchers know a great deal about the negative effects of solitary confinement. We have firsthand or autobiographical accounts by former prisoners (e.g., Burney 1961) and staff members (e.g., Rundle 1973; Slater 1986); ethnographic, interview, and observational research (e.g., Benjamin and Lux 1975; Toch 1975; Hilliard 1976; Jackson 1983; Rhodes 2004; Reiter 2016); and cross-sectional studies that assess prisoners' psychological reactions at particular times (e.g., Grassian 1983; Brodsky and Scogin 1988; Haney 2003).

Much of the important research is qualitative, but there is a substantial amount of it and the findings are robust. They can also be "triangulated," that is, studied through a range of methods and in settings sometimes similar but not necessarily identical to solitary confinement (e.g., Turner, Cardinal, and Burton 2017). Numerous literature reviews have noted that scientists from diverse disciplinary backgrounds, working independently and across several continents, and over many decades, have reached almost identical conclusions about the negative effects of isolation in general and solitary confinement in particular (e.g., Haney and Lynch 1997; Haney 2003; Grassian 2006; Smith 2006; Arrigo and Bullock 2008). Those robust findings are also theoretically coherent. That is, they are consistent with and explained by a rapidly growing literature on the importance of meaningful social contact for maintenance of mental and physical health.

Largely because of the robustness and theoretical underpinnings of the data, numerous scientific and professional organizations have reached

a broad consensus about the damaging effects of solitary confinement. Several years ago, for example, a National Academies of Science committee reviewed the existing research and concluded that solitary confinement can precipitate such "serious psychological change" in prisoners that the practice "is best minimized" (National Research Council 2014, p. 201). The American Psychological Association (2016, p. 1), the world's largest professional association of psychologists, asserted that "solitary confinement is associated with severe harm to physical and mental health among both youth and adults, including: increased risk of self-mutilation, and suicidal ideation; greater anxiety, depression, sleep disturbance, paranoia, and aggression; exacerbation of the onset of pre-existing mental illness and trauma symptoms; [and] increased risk of cardiovascular problems."

Similarly, the National Commission on Correctional Health Care (2016), a highly respected organization of correctional medical and mental health professionals, promulgated a series of "principles" with respect to solitary confinement. They are intended to guide the ethical conduct of its members, including that placement in solitary confinement for longer than 15 days represents "cruel, inhumane, and degrading treatment" that is "harmful to an individual's health" (p. 260) and that "health care staff must advocate" to remove persons from solitary confinement whenever "their medical or mental health deteriorates" (p. 261).

Summarizing this growing consensus, a joint 2016 statement of the Association of State Correctional Administrators (the largest professional association of American prison administrators) and Yale Law School's Liman Public Interest Program observed that demands for change in use of solitary confinement are being made around the world. More specifically,

> Commitments to reform and efforts to limit or abolish the use of isolating confinement come from stakeholders and actors in and out of government. Documentation of the harms of isolation, coupled with its costs and the dearth of evidence suggesting that it enhances security, has prompted prison directors, legislatures, executive branch officials, and advocacy groups to try to limit reliance on restricted housing. Instead of being cast as the solution to a problem, restricted housing has come to be understood by many as a problem in need of a solution. (Association of State Correctional Administrators and the Arthur Liman Public Interest Program 2016, p. 15)

Even more recently, the director of the Colorado Department of Corrections, Rick Raemisch, announced that Colorado has ended use of long-term solitary confinement, so that even prisoners "who commit serious violations like assault will now spend at most 15 days in solitary" (2017, p. A25). This development in Colorado is especially notable, for reasons that become clear in the pages that follow.

Against this backdrop, in 2009 and 2010 word began to circulate among prison researchers and policy makers that a new, supposedly unassailable scientific study—the "Colorado study"—had produced results that contravened many decades of empirical findings on the harmful effects of prison isolation. Lovell and Toch (2011, p. 3) characterized a number of its findings as "flabbergasting," and indeed they were. Among the most startling were that a year-long stay in solitary confinement resulted in no "significant decline in psychological well-being over time"; that on most measures, including cognitive performance, "there was improved functioning over time"; and most remarkably that many more mentally ill prisoners benefited from isolation than were damaged by it (O'Keefe et al. 2010, pp. 54, 78). The Colorado researchers thus reported data indicating that solitary confinement made prisoners feel and think better, especially if they were mentally ill.

In fact, however, the Colorado study was riddled with serious methodological problems that limited its value and made the meaning of the results impossible to decipher. Notwithstanding its authors' frank, albeit at times opaque and oblique, acknowledgments of some of its fundamental weaknesses, defenders of solitary confinement have seized on it. It has become a last bastion of resistance against a widespread and growing consensus that use of solitary confinement should be eliminated or drastically limited.

The Colorado study's influence has been amplified by an equally flawed meta-analysis that relied very heavily on it and significantly mischaracterized the prior literature on the effects of isolated confinement (Morgan et al. 2016). Of course, the influence of a fundamentally flawed study can grow if it and the data it produced are included in literature reviews that overlook glaring weaknesses. This risk is greater in meta-analytic than in narrative literature reviews that focus on decontextualized "effect sizes" irrespective of methodological shortcomings of individual studies. Unlike narrative reviews, meta-analyses include only quantitative outcomes or effects. This elevates the importance of numerical outcomes and often

scants nuanced assessments of data quality. This is particularly a problem for prison research, an enterprise that is fraught with emotional and methodological challenges, in which aspects of the institutional context or setting can fundamentally alter the nature of the research and the meaning of its results. That is precisely what happened in the Morgan et al. (2016) meta-analysis.

In the following pages, I first discuss the scientific basis for the broad consensus that solitary confinement has substantial negative psychological effects on prisoners. I then discuss the Colorado study and the Morgan et al. (2016) meta-analysis based largely on it. Both are textbook examples of how things can go terribly wrong when researchers fail to take account of the unique nature of the prison environment, the special emotional and methodological challenges of prison research in general, and the contingent and unpredictable conditions and practices that affect solitary confinement units in particular.

I. Solitary Confinement Research and Practice

Documentation of the damaging nature and psychological effects of solitary confinement has a very long history, dating at least to the early nineteenth century, when solitary confinement was the modal form of imprisonment. The notion that prisoners could be reformed—made "penitent"—by time spent in isolation dominated American correctional thinking and practice and eventually spread throughout Europe. Yet the practice was recognized as a dangerous failure not long after its inception. Haney and Lynch (1997), Toch (2003), Grassian (2006), and Smith (2006) reviewed much of the early historical literature. Reports on solitary confinement at Pentonville Prison in England described "twenty times more cases of mental disease than in any other prison in the country" (Hibbert 1963, p. 160). Accounts of solitary confinement in the Netherlands documented "again and again, reports of insanity, suicide, and the complete alienation of prisoners from social life" (Franke 1992, p. 128). Newspaper reports from Philadelphia observed that prisoners in solitary confinement at the Walnut Street Jail "beg, with the greatest earnestness, that they may be hanged out of their misery" (Masur 1989, p. 83). Charles Dickens concluded that a prisoner kept in that "melancholy house" was like "a man buried alive . . . dead to everything but torturing anxieties and horrible despair" (Dickens 1842, p. 116). A similar regime in Auburn, New York, was described as "a hopeless failure that led to a

marked prevalence of sickness and insanity on the part of convicts in solitary confinement" (Barnes 1921, p. 53). Stuart Grassian (2006, pp. 342–43) reported that "between 1854 and 1909, thirty-seven articles appeared in German scientific journals on the subject of psychotic disturbances among prisoners." The "most consistent factor" accounting for prison psychoses, "reported in over half the total literature, was solitary confinement."

Systematic early studies of solitary confinement in the United States used what is now seen as a somewhat outmoded theoretical framework, focusing narrowly on sensory rather than social deprivation (e.g., Scott and Gendreau 1969; Gendreau et al. 1972). Even so, the authors of one early study concluded that "excessive deprivation of liberty, here defined as near complete confinement to the cell, results in deep emotional disturbances" (Cormier and Williams 1966, p. 484). In a review of the sensory deprivation literature, Haney and Lynch (1997) noted that "the dissimilarities between conditions created in these studies and those in solitary confinement or punitive segregation in correctional institutions are obvious." They also observed that, nonetheless, the early research did "emphasize the importance of sensory stimulation in human experience and the dramatic effects that can be produced when such stimulation is significantly curtailed" (p. 502).

More recent research focuses on the psychological damage that results from social deprivation. Hans Toch's large-scale psychological study of prisoners in crisis in New York State correctional facilities included important observations about the effects of isolation. After conducting numerous in-depth interviews, Toch (1975, p. 54) concluded that "isolation panic" was a serious problem in solitary confinement. The symptoms Toch described included rage, panic, loss of control and breakdowns, psychological regression, and build-ups of physiological and psychic tension that led to incidents of self-mutilation. He noted that isolation panic could occur under other conditions of confinement but that it was "most sharply prevalent in segregation." Moreover, it marked an important dichotomy for prisoners: the "distinction between imprisonment, which is tolerable, and isolation, which is not."

Empirical studies have identified a wide range of frequently occurring adverse psychological reactions to solitary confinement.[2] These include

[2] For reviews of the literature documenting these adverse reactions, see Haney and Lynch (1997), Haney (2003), Cloyes et al. (2006), Grassian (2006), Smith (2006), and Arrigo and Bullock (2008).

stress-related reactions (such as decreased appetite, trembling hands, sweating palms, heart palpitations, and a sense of impending emotional breakdown); sleep disturbances (including nightmares and sleeplessness); heightened levels of anxiety and panic; irritability, aggression, and rage; paranoia, ruminations, and violent fantasies; cognitive dysfunction, hypersensitivity to stimuli, and hallucinations; loss of emotional control, mood swings, lethargy, flattened affect, and depression; increased suicidality and instances of self-harm; and, finally, paradoxical tendencies to further social withdrawal.

The prevalence of psychological distress, at least as suffered in certain solitary confinement settings, appears to be extremely high. A study conducted at the Security Housing Unit (SHU) at Pelican Bay State Prison in California (Haney 1993; Reiter 2016), an especially severe solitary confinement facility, is illustrative. Structured interviews were used to assess a randomly selected, representative sample of 100 prisoners to determine the prevalence of symptoms of psychological stress, trauma, and isolation-related psychopathology (Haney 2003). The interviews included demographic questions, brief social and institutional histories, and systematic assessments of 25 items, based in part on the Omnibus Stress Index (Jones 1976) and on other instruments similar to those used in Brodsky and Scogin (1988). Every symptom of psychological stress and trauma but one (fainting) was experienced by more than half of the assessed prisoners; many were reported by two-thirds or more and some by nearly everyone. Well over half of the prisoners reported distress-related symptoms—headaches, trembling, sweaty palms, and heart palpitations.

High numbers of the Pelican Bay SHU prisoners also reported suffering from isolation-related symptoms of pathology. Nearly all reported ruminations or intrusive thoughts, oversensitivity to external stimuli, irrational anger and irritability, difficulties with attention and often with memory, and a tendency to withdraw socially. Almost as many reported symptoms indicative of mood or emotional disorders: concerns over emotional flatness or losing the ability to feel, swings in emotional response, and feelings of depression or sadness that did not go away. Finally, sizable minorities reported symptoms that are typically associated only with more extreme forms of psychopathology—hallucinations, perceptual distortions, and thoughts of suicide.

Social withdrawal, a common reaction to solitary, is related to a broader set of social pathologies that prisoners often experience as they attempt to

adapt to an environment devoid of normal, meaningful social contact. In order to exist and function in solitary confinement, where day-to-day life lacks meaningful interaction and closeness with others, prisoners have little choice but to adapt in ways that are asocial and, ultimately, psychologically harmful.

A large international literature has reached similar conclusions on the adverse psychological effects of solitary confinement. Solitary confinement not only is a common form of mistreatment to which prisoners of war have been subjected and been adversely affected (e.g., Hinkle and Wolff 1956) but also is associated with "higher levels of later life disability" among returnees (Hunt et al. 2008, p. 616). It is frequently used as a component of torture (e.g., Foster, Davis, and Sandler 1987; Nowak 2006; Reyes 2007). Solitary confinement has been studied in more traditional international criminal justice contexts as well. For example, Barte (1989, p. 52) concluded that solitary confinement in French prisons had such "psychopathogenic" effects that prisoners placed there for extended periods could become schizophrenic, making the practice unjustifiable, counterproductive, and "a denial of the bonds that unite humankind."

Koch (1986, pp. 124–25) studied "acute isolation syndrome" among detainees in Denmark that occurred after only a few days in isolation and included "problems of concentration, restlessness, failure of memory, sleeping problems and impaired sense of time and ability to follow the rhythm of day and night." If isolation persisted for a few weeks or more, it could lead to "chronic isolation syndrome," including intensified difficulties with memory and concentration, "inexplicable fatigue," a "distinct emotional liability" that included fits of rage, hallucinations, and the "extremely common" belief among prisoners that "they have gone or are going mad."

Volkart, Dittrich, et al. (1983) studied penal isolation in Switzerland. They concluded that, compared with prisoners in normal confinement, those in solitary displayed considerably more psychopathological symptoms, including heightened feelings of anxiety, emotional hypersensitivity, ideas of persecution, and thought disorders (see also Waligora 1974; Volkart, Rothenfluh, et al. 1983; Bauer et al. 1993).

The major reviews of the literature reach the same conclusions as the seminal studies. Haney and Lynch (1997, pp. 530, 537) noted that "distinctive patterns of negative effects have emerged clearly, consistently, and unequivocally from personal accounts, descriptive studies, and sys-

tematic research on solitary and punitive segregation." The "psychologically destructive treatment" to which prisoners are exposed in solitary confinement is so severe that it likely "would not be countenanced for any other group in our society."

Grassian's extensive survey of solitary confinement research concluded that "the restriction of environmental stimulation and social isolation associated with confinement in solitary are strikingly toxic to mental functioning, including, in some prisoners, a stuporous condition associated with perceptual and cognitive impairment and affective disturbances" (2006, p. 354).

That same year, Smith's comprehensive review concluded that "the vast majority" of studies on the effects of solitary confinement "document significant negative health effects" (2006, p. 456). He observed that "research on effects of solitary confinement has produced a massive body of data documenting serious adverse health effects" (p. 475) including "anger, hatred, bitterness, boredom, stress, loss of the sense of reality, suicidal thoughts, trouble sleeping, impaired concentration, confusion, depression, and hallucinations" (p. 488).

Similarly, Arrigo and Bullock (2008) concluded that "nearly all investigators acknowledge that long-term segregation, mistreatment by correctional staff, and preexisting psychological vulnerability are all apt to result in negative mental health consequences for convicts" and that "the extreme isolation and harsh conditions of confinement in [solitary confinement] typically exacerbate the symptoms of mental illness" (p. 632).

There is an important, theoretically coherent framework that helps explain the consistency of these conclusions. A burgeoning literature in social psychology and related disciplines shows that solitary confinement is a potentially harmful form of sensory deprivation but also, and more destructively, exposes prisoners to pathological levels of social deprivation. Numerous studies have established the critical psychological significance of social contact, connectedness, and belonging (e.g., Fiorillo and Sabatini 2011; Hafner et al. 2011; Cacioppo and Cacioppo 2012). Meaningful social interactions and social connectedness can have a positive effect on people's physical and mental health in settings outside of prison and, conversely, social isolation in general can undermine health and psychological well-being. Thus, it makes sound psychological sense that exposure to especially severe forms of material, sensory, and social deprivation harms prisoners' mental health.

Indeed, researchers have concluded that human brains are "wired to connect" to others (Lieberman 2013). Thwarting the need to establish and maintain connections to others undermines psychological well-being and increases physical morbidity and mortality. Because "social connection is crucial to human development, health, and survival," experts have called for it to be recognized as a national public health priority (Holt-Lunstad, Robles, and Sbarra 2017, p. 527). The involuntary, coercive, hostile, and demeaning aspects of solitary confinement are likely to exacerbate the negative effects of social isolation that have repeatedly been documented in more benign contexts.

Given these long-standing and theoretically informed findings, a study purporting to show that psychological effects of solitary confinement range from harmless to beneficial would normally not be taken seriously. Sometimes, however, the appearance of seemingly objective scientific findings provides legitimacy to doubtful conclusions, especially when they support contested policy or political agendas. That is precisely what happened in the case of the Colorado study. Its authors described it as a scientific advance over all previous studies, and some commentators prematurely lauded its methodological rigor. It appeared on the surface to be an ambitious and well-designed longitudinal study, with appropriate comparison groups and a host of dependent variables that were to be examined. Data were collected through the repeated administration of instruments said to be validated, and an unusually large number of prisoners were to be assessed over a 1-year period.

The reality was very different. The project could not be, and was not, carried out as planned, partly because of powerful demands and correctional contingencies inherent in prison settings in general and solitary confinement in particular. The problems proved insurmountable: comparison groups were not comparable, and the integrity of the "treatments" each group received was quickly corrupted. I discuss these and numerous other problems in the next section. The fundamental methodological flaws that plagued the study prevented collection of any meaningful data and ensured that no meaningful conclusions could be drawn.

The Colorado study nonetheless has continued to play an outsized role in contentious policy debates in which proponents of solitary confinement draw on it to support positions that are becoming indefensible. Defenders have characterized the study as "an outstanding example of applied correctional research" that was "planned with great care," em-

ployed a "rigorous" design, and produced results that "were about as conclusive as possible" showing that solitary confinement has few or no adverse effects (Gendreau and Labrecque 2016, p. 9).

A year after the study's release, the National Institute of Corrections devoted an entire issue of *Corrections and Mental Health* to discussion of it. One writer (other than the Colorado researchers themselves) who endorsed its results and defended its methodology was Paul Gendreau, a well-known Canadian researcher and long-time prison system employee. Despite not having published primary research data on isolation since the early 1970s, he had defended its use over many decades, for example, in a 1984 article entitled "Solitary Confinement Is Not Cruel and Unusual: People Sometimes Are!" (Gendreau and Bonta 1984). In *Corrections and Mental Health*, Gendreau hailed the Colorado study as a "truly significant contribution to our knowledge base about the effects of prison life for one of the most severe forms of incarceration" and asserted that "in terms of its methodological rigor" no other study "comes close" (Gendreau and Theriault 2011, p. 1). Moreover, despite the deep skepticism voiced by all of the other contributors to the special issue except Gendreau and the study's authors, the journal's editor described the Colorado study as "an important report" because it showed that "administrative segregation is not terribly harmful" (Immarigeon 2011, p. 1).

Similarly, when a brief summary of the study appeared in a scholarly journal (O'Keefe et al. 2013), it was accompanied by commentary written by several prominent clinicians who claimed to have witnessed as much as or more psychological improvement among isolated prisoners than decompensation. They praised the study as "groundbreaking" and described its methodology as "solid" (Berger, Chaplin, and Trestman 2013, pp. 61–63). The authors averred that "the extremes of solitary confinement have been misunderstood" and that "people are resilient and are able to thrive under even difficult environmental conditions."

The respected Irish prison researcher Ian O'Donnell, though more circumspect, offered similar observations. Although O'Donnell acknowledged some limitations, he praised the study's methodology and invoked its results to support some of his own views. "However unpalatable they might appear to some parties," he asserted, the study's findings "must be taken seriously" (2014, p. 120). O'Donnell characterized the study as "valuable" because, he said, it "highlights the individual's capacity to adapt" (p. 122). He defended the Colorado researchers against criticism, noting that it is ethically impossible to study solitary confinement with "suffi-

cient scientific rigour to satisfy everyone" (p. 122). The study's results suggest, he wrote, "that segregation was not highly detrimental to those forced to endure it" (p. 120) and that the harmfulness of this form of penal confinement "may have been over-emphasized" (p. 123).[3]

The Colorado study also figures prominently in correctional policy reviews by recalcitrant prison officials who do not want to modify segregation practices and in litigation over the harmful effects of solitary confinement, where those defending it are eager to find support.[4] For example, the US Government Accountability Office conducted a review of segregated housing practices in the federal Bureau of Prisons (BOP): "BOP HQ officials cited the 2010 DOJ-funded study of the psychological impact of solitary confinement in the Colorado state prison system. This study showed that segregated housing of up to 1 year may not have greater negative psychological impacts than non-segregated housing on inmates. While the DOJ-funded study did not assess inmates in BOP facilities, BOP management told us this study shows that segregation has

[3] O'Donnell indicated that the study documented the "benefits" of solitary, ones he suggested derived from "the many hours spent in quiet contemplation" in solitary confinement units. He also suggested that the results buttressed his own belief that "severe forms of trauma are sometimes accompanied by an improvement in functioning" (p. 123).

[4] For example, consider the "Expert Report by Robert Morgan, PhD, Ashker, et al. v. Governor, et al., Case No.:C09-05796 CW (N.D. Cal.)" submitted under oath to a federal district court. Morgan opined that being housed in extremely harsh solitary confinement (the SHU in California's Pelican Bay State Prison) for "*ten or more continuous years* does not place inmates at substantial risk of serious mental harm" (p. 1; emphasis added), a position that he supported in part by citing the Colorado study. He described the study as "the most sophisticated study to date on the topic" of the effects of solitary confinement, claimed it showed "an absence of adverse effects for segregated inmates" (p. 1), and cited the results of his own meta-analysis (which was incorporated into Morgan et al. [2016], which I discuss later in this essay) to buttress his defense of long-term solitary confinement. Similarly, see the "Expert Report Provided in the Matter of BCCLA and JHS v. AGC, Court No.:S150415" by Jeremy Mills, PhD, filed in support of the continued use of solitary confinement in Canadian prisons. The Colorado study is described by Mills as "quite likely the most sophisticated longitudinal study to date examining the effects of segregation on mentally ill and non–mentally ill offenders" (p. 13). He also characterized meta-analyses like the Morgan et al. meta-analysis, of which he was a coauthor, as "a hallmark of the scientific process" (p. 12). Mills embraced the Colorado study's conclusions as supportive of his own, which were gleaned from his "clinical experience" working in segregation units on behalf of the Canadian Correctional Service. These included his view that both mentally ill and non–mentally ill prisoners usually need only "a few days" of "a period of adjustment" to get used to solitary confinement. He suggested that prisoners placed in solitary confinement "more frequently" forgo the adjustment period entirely because "they are familiar with the environment" (p. 14). Neither Morgan nor Mills acknowledged the Colorado study's numerous fundamental methodological flaws or indicated that the Morgan et al. meta-analysis on which they relied was based primarily on it.

little or no adverse long-term impact on inmates" (Government Accountability Office 2013, p. 39).

The Colorado study's continuing cachet in prison policy making and important legal circles means that its scientific bona fides bear especially careful analysis. Examining and deconstructing its methodology is a tedious but worthwhile exercise because it illustrates the difficulty of honoring norms of scientific rigor in a setting in which conventional research designs are nearly impossible to implement and necessary trade-offs are especially costly to the quality of the data collected. I turn to that exercise in Section II and to a deconstruction of the Morgan et al. (2016) meta-analysis in Section III.

II. Interrogating the Colorado Study

Results of the Colorado study appeared in two versions: a lengthy final report to the National Institute of Justice (O'Keefe et al. 2010) and a short article in the *Journal of the American Academy of Psychiatry and Law* (O'Keefe et al. 2013). I mostly discuss the more detailed National Institute of Justice report.[5] I also draw on two depositions, under oath, of Maureen O'Keefe, the lead researcher, in connection with prisoner litigation concerning Colorado's "supermax" facility (where much of the study was conducted). In response to detailed questions, O'Keefe discussed numerous issues not raised in the report or fully addressed in published exchanges following its release.[6]

Why the study was undertaken is unclear. Neither of the primary researchers had prior experience with solitary confinement. Maureen O'Keefe had a master's degree in clinical psychology but no prior involvement in research on the effects of isolation. Kelli Klebe was a psychometrician who also had no direct experience with solitary confinement (O'Keefe 2010, pp. 13–14). Yet they designed the study (pp. 77–79).

The study's impetus may have come from Larry Reid, warden of the Colorado supermax prison that housed prisoners assigned to administra-

[5] A number of brief but highly critical commentaries by prison researchers also questioned aspects of the methodology: Grassian and Kupers (2011), Rhodes and Lovell (2011), Shalev and Lloyd (2011), and Smith (2011). See also the response to at least some of these criticisms by Metzner and O'Keefe (2011).

[6] The two depositions are Deposition of Maureen O'Keefe, *Dunlap v. Zavaras*, Civil Action no. 09-CV-01196-CMA-MEH, October 5, 2010; and Deposition of Maureen O'Keefe at 96, 101 *Sardakowski v. Clements*, Civil Action no. 12-CV-01326-RBJ-KLM, October 25, 2013.

tive segregation. O'Keefe indicated that Reid "kept pushing for the study to be done" and served as a member of the study's advisory board (2010, p. 51). A few years before the Colorado study was planned, administrators at a Wisconsin supermax had lost a lawsuit over their use of solitary confinement (*Jones 'El v. Berge*, 164 F.Supp. 2d 1097 [W.D. Wis. 2001]), and Reid apparently wanted to avoid a similar decision. As O'Keefe (2013, p. 44) observed, "I believe [Reid's] concern was that Wisconsin had lost the case and it had severely restricted their ability to use administrative segregation."

The Colorado researchers said that they expected to find that administrative segregation had negative psychological effects: "We hypothesized that inmates in segregation would experience greater psychological deterioration over time than comparison inmates, who were comprised of similar offenders confined in non-segregation prisons" (O'Keefe et al. 2010, p. viii). If so, Warden Reid did not appear to share that view. The Colorado Department of Corrections then housed "three times as many people in solitary confinement as the average state prison system" (*Correctional News* 2012, p. 1). Moreover, O'Keefe (2013, p. 46) acknowledged that Reid "was very pro administrative segregation and all of us on the project felt that way."

Psychologist John Stoner, the mental health coordinator at the Colorado supermax prison, also strongly supported administrative segregation and served as a member of the study's advisory board. He had testified in the Wisconsin case that administrative segregation was not "as detrimental to mental health as others have found it to be" (*Jones 'El v. Berge*, p. 1104). Among other things, Stoner said that he was not troubled by Wisconsin's use of "boxcar" cells with solid metal doors that closed off visual contact and muffled sound because he thought they were "necessary for the protection of staff and other inmates" (p. 1104). He also observed in written testimony that prisoners in isolation who appeared to be seriously mentally ill were likely not as sick as other experts indicated; he speculated that they might be malingering. Although Stoner told the court in *Jones 'El v. Berge* that the isolated housing conditions at the prison were entirely appropriate, the judge disagreed. She held that the Wisconsin facility was unconstitutionally harsh for mentally ill prisoners and ordered them removed.

In any event, the Colorado researchers started out with a seemingly good idea and what appeared to be a reasonable research design. They would identify groups of prisoners housed in administrative segregation

(AS) and in the general population (GP), subdivided into those suffering from serious mental illness (MI) and not (NMI). Their psychological status would be tracked for 1 year to determine whether and how the different groups were affected by different conditions of confinement.[7] The characteristics of the AS and GP prisoners were not matched at the outset but were expected to be more or less comparable because all had committed rules violations for which they might have received an AS placement.

Assignments to AS were thus not random. The researchers reported that "placement into AS or GP conditions occurred as a function of routine prison operations, pending the outcome of their AS hearing, without involvement of the researchers. . . . Inmates who returned to GP following an AS hearing were assumed to be as similar as possible to AS inmates and, therefore, comprised the comparison groups" (O'Keefe et al. 2010, p. 17). The prisoners whom prison authorities chose to send to administrative segregation became the treatment group and those returned to the general population became the comparison group (again, with each group subdivided into those identified by the prison system as mentally ill and those not).

Unfortunately, the plan fell apart almost immediately. The prison context and "routine prison operations" fundamentally undermined the research design.

A. Contamination of Treatment and Comparison Groups

The study's implementation was compromised in two fundamental ways. It is important at this juncture to acknowledge the distinction between mere methodological "limitations"—respects in which a study is not perfect—and problems that are so fundamental that they make the resulting data uninterpretable. The two flaws from which the Colorado study suffered were fatal—separately and in combination.

1. *All Participants Were Exposed to the Treatment.* All participants in the study, including those in the comparison group, were initially placed

[7] Data for one group of participants—prisoners "with the most acute psychiatric symptoms" housed at a psychiatric treatment facility where they lived and interacted with one another "on their living unit" (O'Keefe et al. 2010, pp. 14–15)—did not bear directly on the issue of whether and how much prisoners were affected by AS. The researchers included them separately "to study inmates with serious mental illness and behavioral problems who were managed in a psychiatric prison setting" (p. 17). The prisoners in this group were not living in conditions remotely comparable to prisoners housed in conventional GP or AS units.

in "punitive segregation," a severe form of solitary confinement, for unspecified but not insignificant periods, before being assigned to administrative segregation or the general population. "At the time leading up to and during their AS hearing," the researchers acknowledged, "inmates have typically been in segregation" (O'Keefe et al. 2010, p. 8).[8] The reason was that Colorado prison officials were required to hold hearings to determine whether prisoners were guilty of infractions and if so whether AS punishment was warranted. Prisoners in Colorado as elsewhere are placed in special housing while they await the outcomes of their disciplinary hearings, often for days or weeks before the process is complete. Thus, the researchers also noted that "offenders reclassified to AS *remain* in a punitive segregation bed until an AS bed becomes available" (O'Keefe et al. 2013, p. 50; emphasis added).

Although this is routine correctional practice, its methodological implications were disastrous. It meant that all members of the comparison group were exposed to a severe dose of the isolation "treatment" before the study began. O'Keefe et al. (2010, p. 9) indicated that the punitive segregation conditions where prisoners were kept while disciplinary proceedings unfolded were so harsh that they were "only intended to be used for a short period of time." This severity distinguished it from AS, which was intended to be used for much longer periods. Here is how they described punitive segregation:

> Punitive segregation offenders remain in their cell for 23 to 24 hours a day, only coming out for recreation and showers, both of which are located in the living unit. Therefore, most do not leave the unit during their segregation time. Services including meals, library, laundry, and even medical and mental health appointments occur at the cell door. If a situation warrants an offender to be out of cell, the offender is placed in full restraints and escorted to a room within the unit

[8] Why "typically" is unclear. The report indicates that all prisoners (including the GP comparison groups) were placed in some form of isolation before, during, and shortly after their AS hearings. It is hard to imagine a procedure in which a prisoner would be taken directly out of GP, immediately given an AS hearing, and immediately returned to GP, without having spent time in some form of isolated housing. In fact, the authors reported that AS participants "on average completed their initial test 7 days (SD = 7.3) after their AS hearing," that GP participants on average "were tested 16 days (SD = 18.9) after their hearing," and that "on average, 43 percent of inmates . . . [had] been confined in segregation (40 percent in AS groups and 3 percent in GP groups) for an average of 18.2 days (SD = 18.1)" (p. 30). These figures are mathematically impossible. Moreover, they are at odds with O'Keefe's deposition testimony and with a statement in a more recent published "reflection" on the study (O'Keefe 2017).

> where he or she can meet privately. Many offenders do not like being taken out of their cells because of the use of full restraints. Additionally, they may not like leaving their cell because officers may take the opportunity to search the cell for contraband.
>
> Due to the disciplinary nature of punitive segregation, offenders are stripped of most privileges during their stay. Punitive segregation inmates are neither allowed to work nor permitted to participate in programs or education. Furthermore, their televisions are removed, and they cannot order canteen beyond essential hygiene items. (O'Keefe et al. 2010, p. 8)

Punitive segregation prisoners were denied visits, which were considered too labor intensive for prison staff to administer.

In contrast to AS, prisoners in punitive segregation also were denied the opportunity to engage in programming or education and were "unable to begin working their way toward leaving segregation" (O'Keefe et al. 2010, p. 9). Thus, even study participants who wound up in AS likely experienced punitive segregation as a much worse form of treatment.

This initial exposure of all participants to an especially harsh form of solitary confinement in punitive segregation made it impossible to draw meaningful inferences about any separate, subsequent effects of GP versus AS. There can be no comparison group in a study in which all of its participants are subjected to a harsh form of the treatment whose effects are being measured.

It is impossible to know whether or how control group prisoners were damaged by the time spent in punitive segregation and whether those effects continued throughout the study. Nor could anyone know whether the AS prisoners were actually relieved to enter the "treatment" because it was less harsh than punitive segregation. These imponderables could account for participants' psychological reactions, including the reported lack of differences between the AS and GP groups and the reported "improvement" or lack of deterioration of many members of the AS group. This was thus no longer a study of administrative segregation compared with no administrative segregation, but of varying and unspecified amounts of segregation experienced by everyone.

A different kind of analysis might have salvaged something by using the exact periods of overall exposure to administrative segregation–like conditions (including time in punitive segregation) as a continuous variable to estimate whether duration had an effect. However, the amount of time in segregation each prisoner experienced is not reported, so this

kind of analysis was apparently not conducted. O'Keefe et al. (2010) treated their data as if they had done a classic treatment versus no treatment study, even though they had not.

The likelihood that initial exposure to punitive segregation conditions had significant negative psychological effects on most participants is more than just speculation. The National Institute of Justice report acknowledged that three of the four groups "showed symptoms that were associated with the SHU syndrome" from the outset (O'Keefe et al. 2010, p. viii), which seems a clear indication that the initial period of segregation adversely affected participants before their AS terms began. High levels of psychological distress measured during or after the prisoners' initial exposure to punitive segregation continued throughout the study. O'Keefe emphasized in a deposition that prisoners in all groups reported "pretty high elevations" of psychological distress (2010, p. 171) and that "clearly, very clearly, the offenders responded with very high elevations. They reported high levels of psychological distress" (p. 201).

Symptoms of distress were so elevated that the researchers wondered, and tried to test, whether the prisoners were malingering: "We had this huge rate of offenders who looked like they could be malingering" (O'Keefe 2013, p. 89). O'Keefe recognized, however, that high scores on a malingering scale "could indicate a lot of psychological problems." In the end, the researchers "didn't really believe that [the prisoners] were malingering" and discarded the results of the malingering scale without analyzing them (p. 89).

Thus, although the researchers acknowledged that most of the participants began the study very much affected by emotional and behavioral trauma, they seem not to have considered that much of that trauma resulted from time spent in the punitive segregation units. Nor did they consider that, when participants "naturally got better as time went on" (O'Keefe 2013, p. 91), it was likely because the conditions of punitive segregation that all of them had experienced were now alleviated, even for those who ended up in AS.

The amount of time that the study participants spent in punitive segregation was problematic, especially because even very brief periods of isolation can have damaging psychological effects. The United Nations Special Rapporteur on Torture, Juan Mendez, has noted that "it is clear short-term solitary confinement can amount to torture or cruel, inhuman, or degrading treatment" and recommended that solitary confinement "in excess of 15 days should be subject to an absolute prohibition"

(2011, p. 23). The United Nations adopted that recommendation in the "Mandela Rules," which defined "prolonged solitary confinement" as lasting "for a time period in excess of 15 consecutive days," and mandated prohibition of such prolonged confinement (Commission on Crime Prevention and Criminal Justice 2015, rules 43.1, 44). The National Commission on Correctional Health Care (2016) also characterized "prolonged solitary confinement" lasting for more than 15 days as "cruel, inhumane, and degrading treatment" because it is "harmful to an individual's health" (p. 260). Yet all of the prisoners in GP and AS experienced a nontrivial duration or dose of isolation that lasted well beyond this potentially damaging threshold. A key table in the National Institute of Justice report indicated that, at the time of their first test interval, participants had spent considerable average times in "Other seg": GP MI prisoners 12.4 days, GP NMI 39.8 days, AS MI 88.9 days, and AS NMI 90.3 days (O'Keefe et al. 2010, table 5).

In her deposition testimony, O'Keefe could not remember exactly how long study participants remained in punitive segregation before their charged disciplinary infractions were resolved. At one point, she said, "When an offender acted out, they were put in punitive seg and generally given notice of a hearing pretty quickly, and then the hearing happened, again pretty quickly after that" (2013, p. 93). Later she "guessed" the time was around "the two week mark" (p. 94). That was not remotely accurate, according to table 5 in the report, except for the GP MI group. O'Keefe later offered another estimate, this time that prisoners were kept in various punitive segregation units "an average of 30 days" before their initial testing session (2017, p. 2). This, too, is much less time than the National Institute of Justice report showed. In any event, it appears that all study participants were subjected at the outset to harsh conditions of punitive segregation for at least twice as long as the Mandela Rules would prohibit, even before the study officially began.

2. *Uncontrolled Cross Contamination.* The second fundamental flaw was as important as the first. It, too, occurred because placement and retention in AS were correctional rather than methodological decisions. The researchers admitted that they "lack[ed] control over the independent variable, which in this case is the conditions of confinement" (O'Keefe et al. 2010, p. 35). There was, in their words, "contamination across groups," because some AS participants "were not confined in segregation for their entire period of participation in the study" and because some GP participants "may have at some time during their study partic-

ipation been placed in punitive segregation or even AS" (p. 35). The researchers also acknowledged that prisoners in the various subgroups "may have [been in] multiple locations within a study period" (p. 35).[9] In fact, not only did participants move between AS and GP, but a number of them were housed in other conditions during the study, including the hospital and "community placement" (p. 36).

Transferring prisoners back and forth between locations and custody statuses is routine correctional practice, but it had disastrous methodological consequences. It meant that some AS prisoners in the study were released into GP for good behavior, some GP prisoners were placed in AS (or punitive segregation) for rule violations, and some members of both groups were transferred to other settings. Having both control and experimental group members move back and forth between treatment and control conditions (and other unspecified places) destroyed the integrity of the two groups and made it impossible to compare their experiences meaningfully.

The contamination occurred differently between groups. By the end of the study, only small and very different numbers of "uncontaminated" participants were left in each group.[10] Methodologically speaking, a true, a natural, or even a quasi experiment cannot be completed if researchers lose control of the integrity of their treatment and comparison groups. The researchers, however, simply aggregated the contaminated prisoners' data into the groups in which they were originally placed.

O'Keefe et al. (2010, p. 35) acknowledged that "one of the challenges of applied research is the researchers' lack of control over the independent variables," but that admission does not ameliorate the problem. They

[9] They wrote that "participants remained in their assigned group regardless of their placements throughout the prison system" (O'Keefe et al. 2010, p. 35), but mean by this that individual prisoners were considered to be in those groups for purposes of data analyses even though they did not actually remain housed there.

[10] There were only 26 "pure" cases in the AS MI group (of the original 64), 39 in AS NMI (of 63), 13 in GP MI (of 33), and only 11 in GP MI (of 43) (O'Keefe et al. 2010, p. 35). All the others moved back and forth between treatment, control, and miscellaneous other conditions on an unspecified number of occasions. Thus two-thirds (52 of 76) of the GP control participants spent time in segregation or other non-GP settings during the study period, and their self-reports were used to contrast their prison experiences and reactions with those of the AS prisoners, half of whom (62 of 127) spent unspecified amounts of time in GP or elsewhere. The "pure" cases were pure only in the sense that they were not contaminated by moving back and forth between treatment, control, and other conditions during the study. They were still "contaminated" by being exposed to punitive segregation before the study officially began.

nonetheless asserted that "a significant advantage of this study is the use of comparison groups to determine if [persons in AS] change over time differentially compared to similar groups who are not placed in AS" (p. 59). However, they did not compare similar groups and thus can reach no conclusions about differences in the groups' experiences.

In fact, it is impossible to conclude anything meaningful from the Colorado results. Lovell and Toch (2011, p. 4) in their initial commentary on it correctly concluded that "despite the volume of the data, no systematic interpretation of the findings is possible."

B. Additional Serious Flaws

The researchers' inability to maintain control of key aspects of their research created numerous additional methodological problems. These problems further negated the possibility that any credible or meaningful findings would emerge from the study.

The additional problems pertained to how the participants were selected and how the various groups were composed, what the researchers recorded (or failed to record) about the experiences of members of the different groups, and questionable data collection procedures. Most stemmed from unyielding correctional realities and some from unwise methodological choices.

1. *Sampling and Group Composition.* The initial sample was drawn from among prisoners deemed eligible for the study by virtue of having received a disciplinary write-up and scheduled hearing to determine whether they would be placed in AS or returned to GP. The initial group of eligible prisoners was much larger than the number selected to participate. The decision about whom to approach was made single-handedly and, as she would characterize it, "haphazardly" by O'Keefe: "I would determine who we used, who we included in our study" (2010, p. 116).

The major consideration for inclusion was proximity to the field researcher: "We had one researcher, so we had to be able to manage her workload" (O'Keefe 2010, p. 116). She described the process as "haphazard selection. . . . We didn't do it in a random fashion, but we didn't necessarily do it in a very targeted fashion either" (p. 116). Participants were drawn from only 10 of Colorado's 26 men's GP prisons (O'Keefe et al. 2013, p. 51). A disproportionate number came from Limon Correctional Facility "[because] it's fairly close" (O'Keefe 2013, p. 66). This was not mentioned in either the National Institute of Justice report or

the briefer published version of the study. If there was anything significantly different about that prison, for example, if its punitive segregation unit (where participants were housed before the study began) was especially harsh or its GP units (to which many participants were returned) were particularly dangerous, troubled, or inhumane, then a disproportionate number of prisoners would have been affected by being held there.[11] There is no way to tell.

There was also unexplained and unnecessary imprecision in the composition of the groups. In addition to being composed of persons subjected to punitive segregation immediately before they entered GP, the GP group began as an amalgam of prisoners who subsequently lived under different conditions of confinement. Thus, "thirteen participants in the GP groups were selected from the diversion program (for being at risk of AS placement)" (O'Keefe 2010, p. 30). The report elsewhere implied that all of the prisoners were at risk of AS placement because all had AS hearings; apparently that was not true, and some were "diverted" out of the process entirely.

A potentially more serious problem concerned the composition of the AS group. O'Keefe et al. (2010, p. 8) asserted that "Colorado does not house protective custody; therefore, no AS placements occur at the request of inmates." This is a correctional non sequitur. Colorado may not officially house protective custody inmates, but they exist in every American prison system. Protective custody inmates often end up housed in AS, whether or not they formally request it. In the Colorado study, an unusually large group of AS participants were identified as having sex offender needs: 30 percent of the AS NMI prisoners and 44 percent in the full AS group (p. 45). In other prison systems, many, possibly all, such prisoners would be protective custody cases. To be sure, protective custody prisoners are subject to the painful and potentially harmful effects of social and sensory deprivation. However, they are in a very different situation psychologically than prisoners placed in AS for punishment. Protective custody prisoners typically prefer to be housed in AS-type conditions instead of what they regard as more dangerous GP environments. As a result, they are likely to be reluctant to voice complaints about living

[11] O'Keefe understood the implications of the sampling methods. Concerning work by others on the effects of administrative segregation, she wrote, "Of particular concern is that sampling procedures are often not discussed, and thus it is impossible to know if the findings were based on a representative sample" (2008, p. 127).

conditions or adverse emotional reactions, lest they be moved. That a third of the AS NMI prisoners and nearly half of the AS group overall in the Colorado study were probably protective custody cases undermined any straightforward interpretation of the data.

Gang members presented a similar problem. Thirty percent of AS MI prisoners and 43 percent of those in the AS NMI group were identified as gang members (O'Keefe et al. 2010, table 9). Being a gang member would ordinarily reduce a prisoner's willingness to report psychological distress because that would be a sign of vulnerability that might be interpreted as weakness.

Thus, nearly three-quarters of both the mentally ill and non–mentally ill AS prisoners were likely protective custody cases or gang members. Yet the researchers ignored the implications of this entirely.

2. *Uncontrolled Differences in GP Conditions.* The control condition—GP—referred to placement in one of 10 different prisons. However, none of the specific conditions of confinement at any of those prisons is described.[12] Variations in GP environments matter because, obviously, unless all GP prisoners experienced the same environment, they were not really in the same condition. If some of the GP environments were so troubled, dangerous, and harsh that they approximated or were worse than conditions in AS, it would be impossible to make meaningful comparisons.

A disproportionate number of study participants were housed in the Limon Correctional Facility (O'Keefe 2013, p. 66). This appears to have been an especially troubled prison when the study was conducted. In 2010, a journalist wrote about "Limon's long history of inmate violence, including two fatal stabbings in five years and the beating death of a correctional officer" (Mitchell 2010).[13] The prison's 5-year violent history encompassed the entire period of the Colorado study from July 2007 through March 2010 (O'Keefe et al. 2010, p. vii). This meant that many study participants came from (and GP comparison group prisoners remained in) an especially harsh and dangerous GP environment, perhaps one as psychologically stressful as an AS unit. In fact, Limon's vi-

[12] The published article indicated only that "GP inmates have access to significant out-of-cell time (e.g., >10 hours/day), jobs, and programming" (O'Keefe et al. 2013, p. 51). No additional information about the GP environments was provided.

[13] There were also allegations that in 2008 sex offenders at the prison were targeted by gang members who extorted them to pay "rent" and repeatedly threatened and assaulted them (*Davis v. Zavaras*, 2010 WL 625043 [D. Colorado 2010]).

olent history may have been serious enough to have precipitated recurring violence-related lockdowns (e.g., Associated Press 2007), including in the GP units where some of the control inmates were housed. None of this was commented on or taken into account.

3. *Uncontrolled Differences in AS Conditions.* Colorado study AS participants were ostensibly in the same study condition but were nonetheless exposed to very different conditions of confinement. These differences were not recorded or quantified and thus could not be taken into account. First, as I noted, all study participants experienced varying amounts of a harsh form of prison isolation, punitive segregation, before the study began. For a significant number (apparently, the majority) of the AS prisoners, that continued for a quarter or more of the length of the study. Thus, "When the study began, there was a 3-month average wait for inmates to be transferred to [AS]," which was "due to a shortage of beds. While on the waitlist, AS inmates were held in a punitive segregation bed at their originating facility" (O'Keefe et al. 2010, p. 19).

The median stay in punitive segregation for AS participants was reported as 99 days (which means that half were longer), although a very small group of prisoners were moved "quickly" into AS. Despite these very different periods in prestudy punitive isolation, all AS participants were lumped together for purposes of analysis.[14]

There was additional imprecision about how much and what kind of isolation any one AS participant experienced. Some "were not confined in segregation for their entire period of participation in the study" but were released into GP or other less onerous settings (O'Keefe et al. 2010, p. 19).

However, even beyond this, it is impossible to know exactly what conditions of confinement were experienced by participants who remained in AS throughout the study. The reason is that Colorado's AS program operated a "level" system in which a prisoner's "quality of life" (QOL) varied as a function of behavioral compliance and programming. Changes in QOL were meant to be incentives for compliance with unit rules and eventual reassignment to GP. The average length of AS stay was said to be 2 years, with the expectation that prisoners would spend at least 1 year in AS. However, the minimum stays specified for the QOL program

[14] The "distance between when they were ad-seged and when they went to CSP became longer and longer because of the wait list in DOC" (O'Keefe 2010, p. 108). An unspecified but not insignificant number of administrative segregation prisoners "were held in the punitive segregation bed but classified as ad-seg. And that's the—for the study average to be about 90 days, but people could be there pretty short, pretty long" (p. 109).

envisioned much shorter stays: 7 days at level I, 90 at level II, and 90 at level III—187 days altogether—after which prisoners were eligible for consideration for reassignment back to GP (O'Keefe et al. 2010, p. 11).

Providing achievable incentives for good behavior and early release from AS are sensible correctional practices. However, they, too, further compromised any meaningful interpretation of the study results.

This methodological problem was significant because the differences in QOL at different levels of AS were substantial. The researchers acknowledged that "it was expected that [prisoners in AS] might experience varying amounts of isolation based on the amount of time spent at different [QOL] levels" (O'Keefe et al. 2010, p. 40). But these varying amounts of isolation were not documented or taken into account.

O'Keefe acknowledged that the researchers initially wanted information from prison staff on participants' out-of-cell time, "to track every time they left their cell," but could not obtain it because the data "just were not coded consistently or every time" by correctional officers (2013, p. 55). That meant that the researchers were unable to track the basic facts of whether, when, and for how long any one prisoner was at one or another AS level or incorporate these data into their analysis (p. 60). O'Keefe et al. (2010, pp. 40–41) reported that staff records yielded "conflicting information," and "it was often difficult to decipher and/or interpret the records." Thus, "it was not possible to code or use [them] in the study."

4. *Failure to Control or Record Treatment Dose.* There was more to these uncontrolled and unrecorded variations than just minor differences in the amount or duration of isolation. The variations in isolation in the AS condition—including for the relatively few prisoners who stayed in AS continuously—were very significant. The QOL level III AS prisoners were given additional privileges and allowed to have jobs as orderlies or in the barbershop. This permitted significant out-of-cell time, during which the prisoners were presumably unrestrained and in contact with others.[15] These opportunities are rare in prison AS units anywhere and

[15] As O'Keefe et al. (2010, p. 12) noted, "Arguably one of the most important benefits of QOL level three is an offender's ability to have more contact with friends and family. While offenders' visits remain noncontact, they are increased to four 3-hour visits per month and four 20-minute phone sessions. . . . One additional benefit is that offenders may now be eligible to work as a porter or barber. . . . Benefits to being offered a job position include the ability to earn money, increased time out of cell, and two additional phone sessions per month."

constitute a significant modification in the nature of the isolation experienced by an unspecified number of AS prisoners. They introduced even more heterogeneity into the "same" condition in the study than already existed.

The researchers also noted that an AS prisoner who acted out could be even more significantly locked down by being placed "on special controls in the intake unit where he can be carefully monitored" and "additional sanctions may be imposed through the disciplinary process" (O'Keefe et al. 2010, p. 13).

None of these and other variations in actual day-to-day conditions of confinement were taken into account. The researchers also did not record and were unable to estimate other basic, important variations in the experiences and treatment of the study participants. These included the number of social or family visits prisoners had, visits from attorneys (O'Keefe 2010, p. 164), and the nature or amount of mental health services the prisoners (including those who were mentally ill) received. As O'Keefe summarized, "We did not look at any facet of segregation or correctional conditions that might affect the outcome of the study. We merely looked at, based on their conditions of confinement—that is, whether they had originally been coded 'AS' or 'GP'—and then noted 'if they reported worse change over time'" (p. 207). But whether a prisoner had originally been coded AS or GP did not indicate what "conditions of confinement" he had experienced in the course of the study.

C. Miscellaneous Data Collection Problems and Issues

In addition, there were very serious problems with how the Colorado researchers initially structured and eventually implemented the data collection process as well as with the dependent measures they used. Some of these problems were the product of the challenging nature of the prison environment. Others were not.

1. *A Single, Inexperienced Field Researcher.* Almost all the data collection was done by one inexperienced research assistant who had only a bachelor's degree, no graduate training, and no prior experience working with prisoners or in a prison setting. She was single-handedly responsible for conducting five to six separate testing sessions in which she administered between 10 and 12 separate tests with each of 247 participants in 10 different prisons.

The data collection was unusually challenging. O'Keefe noted, "Say when she was at CSP [the AS facility], she might have a whole bunch

of [participants] and she would go back and forth checking to make sure that they were all right, and administering the questionnaires when she needed to" (2010, p. 118). Yet no one oversaw her day-to-day work (p. 130). O'Keefe had no recollection of ever observing her administering the tests and indicated Klebe did not (2013, p. 85).

2. *Solicitation and Consent.* When prisoners' participation and consent were solicited, they were told, somewhat misleadingly, that "we're looking at how inmates across the entire DOC are adjusting to prison life" (O'Keefe 2010, p. 199). O'Keefe characterized this as "being cautious without being dishonest" (p. 200). The consent form told prisoners that the "risks of this study to you are very small in contrast with the benefits that are high. This study will help us to figure out what types of men adjust better to prison and how to help those who are struggling with prison life" (O'Keefe 2013, pp. 81–82). This, too, was misleading. The study was not about the types of men who adjust better to prison and how to help them. Moreover, no consideration was apparently given to the possibility that prisoners might want to appear to be "adjusting" rather than "struggling." This would apply with special force to AS prisoners, hoping to advance their QOL level and with that gain additional privileges and earlier release from the unit.

3. *Prison Employee?* The field researcher had to complete "the full CDOC [Colorado Department of Corrections] training academy" and at all times was required "to wear a visible CDOC badge that permitted her unescorted access to the facilities" (O'Keefe et al. 2010, p. 28). Although O'Keefe was "not sure" how the field researcher introduced herself to prisoners, she conceded that "it could be" that prisoners thought the field researcher was a DOC employee (2010, p. 125).

Prisoners in general, and especially in AS units, are typically reluctant to confide in prison staff (including even mental health staff) because of potential adverse consequences. Those consequences can include increased surveillance, placement in degrading "suicide watch" cells, or transfer to or retention in some other form of AS. For these reasons, prisoners frequently avoid admitting that they feel suicidal, depressed, frightened, angry, panicky, out of control, or violent.

That prisoners could reasonably infer that the field researcher/prison employee was checking on their "adjustment" is likely to have dampened their willingness to disclose sensitive feelings. This possibility is nowhere discussed. Despite the fact that while the study was under way, O'Keefe acknowledged awareness of the fraught nature of prisoner-staff

relations, especially in AS units: "Administrative segregation facilities are characterized by the complete control exerted over inmates by correctional staff. The typical 'we-they' dynamic between inmates and staff is exacerbated in segregated settings where inmates have almost no control over their environment. Prisoner abuses have been discovered and punished in administrative segregation settings, but in other situations Human Rights Watch found that 'management has tacitly condoned the abuse by failing to investigate and hold accountable those who engage in it'" (2008, p. 126; internal citations omitted).

4. *Undermining Trust.* Little was done to overcome what O'Keefe described as the "we-they" dynamic that she believed was likely to be exacerbated in prison AS units. Two related problems with the Colorado study likely exacerbated the effects of this dynamic. The first was an error of omission: no interviews were conducted to establish rapport with prisoners. O'Keefe indicated that "it was not part of the study to probe and ask them [the prisoners] about themselves" (2013, p. 75). Without rapport-building interactions, prisoners in the study were unlikely to have had much confidence that the field researcher was interested in their well-being or that personal revelations would be handled with sensitivity.

The second problem is more troubling. The field researcher was apparently required (or decided on her own) to challenge prisoners if she thought their answers were "questionable" or "untruthful, or if she found the pattern of their responses abnormal" (O'Keefe et al. 2010, p. 36). There was no explicit or systematic protocol by which this judgment was reached (none is described). In any event, the field researcher reviewed the prisoners' responses on the spot, in their presence, every time they completed a questionnaire. If she was skeptical, the prisoner was asked to redo the test. Prisoners could decide to redo the test or not, but "if the participant said he was being honest and the researcher still did not believe him, she marked the test as questionable" (p. 36).

These practices potentially created very significant data quality problems. They not only jeopardized the development of rapport or trust but also increased the chances that prisoners would give situationally desirable answers. In addition, the problems likely extended to more prisoners than only those who were challenged directly, but to other prisoners who learned through word of mouth that they would be asked to redo their questionnaires if the researcher was skeptical of their answers.

5. *"Untruthful" and Other Questionable Data.* Twelve percent of participants "had a questionable response pattern on any measure at any

time period" (O'Keefe et al. 2010, p. 36). It is unclear whether that figure included all participants who were asked about their answers or only those whose answers were marked "questionable." If challenged prisoners admitted being untruthful and redid the questionnaire, the second versions of their answers were incorporated into the study data. However, even if the field researcher was skeptical and prisoners chose not to redo their questionnaires, "we still included that in the study. . . . In order to increase our statistical power . . . we left those cases in" (O'Keefe 2010, p. 166).

In addition, 23 participants withdrew their consent and dropped out before the study was completed. However, their data were retained and used in the overall analyses (O'Keefe et al. 2010, p. 19). The dropouts constituted nearly 10 percent of the 247 participants. This meant that, in total, more than 20 percent of the participants whose data were included in the study results were adjudged to have given untruthful responses or withdrew from the study.

6. *An AS "Heisenberg Effect"?* The repeated testing procedure changed the conditions of confinement, especially for AS prisoners otherwise subject to extreme social deprivation. The six interactions of approximately an hour each between the field researcher and the prisoners, no matter how strained or superficial they might have been, increased the otherwise minimal social contact that AS prisoners had with people outside the segregated housing unit.[16] In many prison systems, there are many AS prisoners who get no visits at all. The mere act of repeatedly attempting to measure the effects of severe conditions of isolated confinement can change them, if only slightly, for the better.

7. *Miscellaneous Issues.* There were other irregular, questionable, and unexplained research decisions and data anomalies. Exactly why prisoners were assigned to AS or GP was not indicated, even though this was how the treatment and control groups were created. Assignment to AS was apparently nearly automatic: no more than "approximately 10 percent of hearings do not result in AS placement" (O'Keefe et al. 2010, p. 17). This raised questions, never addressed, about what accounted for the unusual outcome in the case of the group that was returned to GP.

[16] It apparently exceeded the contact AS MI prisoners had with mental health staff: "Offenders with mental illness who are stable are offered a one-on-one session at least once every 90 days," which takes place "in a noncontact booth in the visiting room" (O'Keefe et al. 2010, p. 11).

Nor were reasons discussed for why the NMI prisoners who returned to GP had more disciplinary infractions (average 16 each) than those sent to AS (13.2 average). Nor were reasons discussed for why AS MI prisoners had 70 percent more disciplinary infractions on average than the AS NMI inmates (22 infractions compared with 13.2; O'Keefe et al. 2010, table 9). Nor was there discussion of the effects of exclusion of prisoners from the study who did not read English at an eighth-grade level on the representativeness of the final group of participants, especially with respect to ethnicity and the prevalence of cognitive impairments.

D. Troubling Dependent Measures

There were also serious problems in the handling of dependent variables in the study. Dependent measures were said to have been selected on the basis of several important criteria. However, the first two criteria the researchers identified—"(1) use of assessments with demonstrated reliability and validity, (2) use of multiple sources for providing information (e.g., self-report, clinician ratings, files)" (O'Keefe et al. 2010, p. 19)—did not apply to the dependent measures that were actually used in the analyses.

1. *Unvalidated Scales and Instruments.* Some of the study's scientific bona fides were based on its claimed use of validated and objective assessment instruments. The researchers asserted that "the use of a reliable and valid standardized measure in the present study enabled objective assessment of psychological functioning" (O'Keefe et al. 2013, p. 57).

Indeed, O'Keefe acknowledged that "inaccurate judgments" could be made if instruments were not properly validated (2010, p. 22). However, she later conceded that only "a very low number" of the numerous scales and measures used, perhaps no more than one or two, had been normed or validated with a prisoner population (pp. 144–45).[17]

[17] There was no evidence that even the Brief Symptom Index (BSI), on which the researchers relied exclusively in the published version of the study, O'Keefe et al. (2013), had ever been validated with a prisoner as opposed to a "forensic" population. One study that the authors cited to support its psychometric properties (Kellett et al. 2003) concerned the BSI's reliability with persons suffering from intellectual disabilities and did not include a representative sample of prisoners (the "forensic" portion of the sample consisted of 45 "intellectually disabled" convicted persons who were "detained in a maximum security hospital" [p. 129]). The second, Boulet and Boss (1991), was a study of "psychiatric inpatients and outpatients who presented for evaluation at the forensic service of a psychiatric hospital" (p. 434). The third, Zinger, Wichmann, and Andrews (2001), focused on prisoners but did not report reliability or validity data for the BSI.

2. *"Constructs" That Could Not Be Interpreted or Compared.* The near-exclusive reliance on prisoners' self-report assessments was problematic because the researchers chose to separate the various scales into their component parts and then recombine items into eight separate "constructs." Instead of reporting scores on the instruments or scales themselves, only the constructs built from them were presented as standardized composite rather than numerical scores (O'Keefe et al. 2010, p. 22). This meant that the significance of reported overall trends and comparisons between groups was, as Lovell and Toch (2011, p. 4) put it, "difficult to assess because of the degree to which the data have been cooked."

There are a number of unanswered questions concerning construction of composite scales including their basic validity (whether the instruments measured what they purported to measure), whether the various subscales were reliable for this population, and whether the distributions of scores lent themselves to the statistical manipulations and recombinations that occurred. Transformations to the data, the number of instruments, items, and constructs, and the amount of scale and subscale reconstruction that occurred make the results difficult to put in the context of any larger literature using the same self-reported assessments.

3. *Ignoring Behavioral Data.* Researchers who use many rating scales (especially ones not validated for the particular population) generally use other methods of data collection as a validity check. The most basic is a face-to-face interview to establish rapport and acquire background information. When possible, behavioral data (by records reviews or behavioral rating scales completed by others) are included. These different sources of information should be reconcilable, and the interviews provide the glue that binds them. Prison researchers typically take things prisoners say to them very seriously, in part because they contextualize other things being measured or studied. However, no interviews were conducted in the Colorado study, and little or no special effort appears to have been expended to establish rapport. Instead, the researchers engaged in context-free coding and analysis of answers on prepackaged forms associated with tests not typically used with this population. As Lovell and Toch (2011, p. 3) observed, "Readers find themselves swimming in a flood of psychometric data; every so often a clue drifts by, lacking, however, a tether to the context—to what was going on around the prisoners and staff while they carried out this study—we are left to guess what it might mean."

Other kinds of data collection were contemplated including asking corrections officers and clinicians to complete rating scales: "The Brief Psychiatric Rating Scale was completed by clinical staff and the Prison Behavior Rating Scale was completed by correctional officers and case managers" (O'Keefe et al. 2010, p. 26). However, key details about this process were omitted (i.e., exactly who was supposed to complete scales, when, and with what kind of training). In the end, it did not matter. The rating scales were infrequently completed and the responses were too unreliable to be useful. The data were discarded. The researchers ultimately relied only on data from prepackaged, field researcher–administered rating scales.

There was one potential exception. Prison mental health staff kept official accounts of genuine psychiatric emergencies or "crisis events." Any situation that required "immediate psychological intervention is considered a crisis event; crisis events are documented by clinicians" (O'Keefe et al. 2010, p. 42). Because these are typically extreme, clinically significant events, they tend to be reliably recorded. If the prisoners' self-reporting was valid, the results should be more or less consistent with behavioral measures of psychological distress or crisis. In the Colorado study, they were not. Among the 33 GP MI prisoners for whom data were reported, there were only three "crisis events" (on average, one for every 11 inmates). Among the 64 AS MI prisoners, there were 37 "crisis events" (one for every two; O'Keefe et al. 2010, figs. 29, 30). This suggests that at least some mentally ill prisoners were doing much worse in AS than their counterparts were doing in GP.

The researchers dismissed the implications of this incongruity: "Because the number of participants who experienced a crisis event was so small, it was not possible to include this variable as an outcome measure in the change over time analyses" (O'Keefe et al. 2010, p. 42). Thus the significant disparity between self-reports and the behavioral measures was ignored, even though it directly contradicted the study's main finding that AS did not adversely affect the mental health of mentally ill participants. Instead, as they put it, because the mental health crisis data "raise more questions than they provide answers," they were deemed "outside the scope of the current research" (p. 42).

In sum, for all of the above stated reasons, the Colorado study is so methologically flawed that literally no meaningful conclusions can be drawn from it. Drastic compromises necessitated by the complex realities of the prison setting and a series of questionable methodological decisions made

by the researchers rendered its results uninterpretable. The Colorado study was not the "most sophisticated" study done to date on the psychological effects of solitary confinement. Its results do not "need to be taken seriously," but cannot be taken for anything at all. Commentators who have praised the study either did not read it very carefully, were unaware of available sources of information on how it was actually conducted, or did not seriously consider the implications of its fundamental flaws.

Ordinarily, a study of this sort would die a quiet death, notwithstanding an occasional prison system's attempt to resuscitate it to defend questionable segregation practices or a scholar overlooking its flaws because its findings comport with his or her own views. However, it has recently been given a second life, figuring prominently in a recently published meta-analysis (Morgan et al. 2016). Its results threaten to live on in another form and to misrepresent the findings of the large, long-established, and frequently reconfirmed literature on the harmful effects of solitary confinement.

III. The Limits and Dangers of Meta-Analysis

Meta-analysis—"a quantitative method of synthesizing empirical research results in the form of effect sizes" (Card 2012, p. 7)—is an important methodological advance that allows researchers to estimate the overall magnitude of relationships between variables. However, it cannot substitute for careful narrative reviews of scientific literature. Meta-analysis comes with substantial limitations, especially for prison research. The prison setting rarely lends itself to collection of meaningful quantitative data capable of generating the kinds of effect sizes on which meta-analyses depend. Most classic book-length treatments of prison life have been primarily ethnographic—not quantitative at all. They contain few if any numerical data, including in the seminal American works by Cressey (1940), Sykes (1958), Toch (1975, 1977), Jacobs (1977), and Irwin (1980) and major comparable British works including Cohen and Taylor (1972) and Crewe (2009).

Similarly, few quantitative effect sizes appear in studies of solitary confinement. This is true of the studies that tell us much of what we know about these institutions, how they operate, and the lengths to which prisoners must go in order to survive inside them, including those from Rhodes (2004), Shalev (2009), Reiter (2016), and Kupers (2017). It is also true of most of the numerous studies of the negative psychological con-

sequences of prison isolation that are discussed in the most-often-cited literature reviews. The nature of the settings and the routine prison operations that govern them make many kinds of conventional research designs impossible to implement.

Because the best prison research is qualitative, or does not lend itself to generating effect sizes, meta-analyses conducted on many important prison topics will be compromised by serious sample bias, resulting in "the drawing of inferences that do not generalize to the population of interest (typically all research conducted on the topic)" (Strube, Gardner, and Hartmann 1985, p. 66).

The concern is not only that meta-analyses on important prison topics almost invariably ignore or underrepresent the larger literature, but also that they privilege certain kinds of studies far beyond their actual scientific merit, and do so in a way that many readers are unlikely to appreciate. One critique rightly observed that readers "might not be motivated to look beyond the meta-analyses themselves due to confidence in the objective, straightforward nature of the tasks of conducting a meta-analysis, reporting findings, and making recommendations" (Coyne, Thombs, and Hagedorn 2010, p. 108). Reducing entire studies to single or multiple effect sizes almost invariably creates a false equivalency between them. Readers can easily be mesmerized by arrays of numbers that appear simply and accurately to represent highly complex and substantially different underlying realities.

The two meta-analyses contained in the Morgan et al. (2016) article suffer from all of these problems and more. They need to be scrutinized carefully because of the stakes involved and the possibility that they will mislead correctional decision makers and policy makers by their "surprising results," ones that, as the authors say, "do not fit with people's intuitive analysis of what happens when you isolate offenders" in solitary confinement. The resulting conclusions are indeed "in marked contrast to the 'fiery opinions' . . . commonly presented in the scientific and advocacy literature" in which solitary confinement "has been likened to torture, with debilitating consequences" (p. 455). They warrant conscientious examination.

A. Truncating the Scope of Literature Reviewed

The first problem with Morgan et al. (2016) is the tiny number and unrepresentative nature of studies included in its two separate meta-

analyses. Literature reviews, whether narrative or meta-analytic, are useful only if they faithfully represent the literature being examined. As Card (2012, p. 10) put it, "If the literature reviewed is not representative of the extant research, then the conclusions drawn will be a biased representation of reality." Morgan et al. (2016) excluded a vast number of published studies, including most of the key works.

The first meta-analysis, "Research Synthesis I," reported that over 90 percent of the published material that they found on the topic was eliminated: "Of the 150 studies located, only 14 (or 9.3 percent) were suitable for analysis according to our inclusion criteria" (Morgan et al. 2016, p. 442). The second meta-analysis, "Research Synthesis II," began with an astonishing 40,589 articles, which were reduced by "trained research assistants" using unspecified methods to 61. A "trained research assistant" then used unspecified methods to reduce that number to 19 (0.05 percent of the initial literature; pp. 442–43).

A meta-analysis that includes so little of the available relevant literature is not a synthesis of much of anything. In addition to the drastic reduction in the sheer number of articles included, the selection criteria used by Morgan et al. (2016) excluded key studies but included questionable other ones. Among the articles excluded is Grassian (1983), regarded as one of the seminal studies on the adverse effects of solitary confinement. Morgan et al. also ignored most of the work discussed in widely cited literature reviews by Haney and Lynch (1997), Haney (2003), Grassian (2006), Smith (2006), and Arrigo and Bullock (2008).

Despite the small numbers of studies included, tables reporting effect sizes seem to suggest that a vast number of studies were taken into account. A closer look reveals something different. Many of the studies have little or nothing to do with the key question of whether and when solitary confinement is psychologically harmful. Morgan et al. (2016) included studies that addressed medical outcomes, and behavioral outcomes such as recidivism and institutional misconduct, that have not been widely studied and are not central to understanding solitary confinement's psychological effects. Thus, despite the drastic reduction in overall number of studies, many of the studies actually included were simply beside the main point.

When the largely irrelevant studies are set aside, only six studies on the psychological effects of solitary confinement remain in the first meta-analysis and 10 in the second. Two in the first were excluded from the sec-

ond and six others were added.[18] No explanation is given for why different sets of articles appeared in the two meta-analyses. In any event, the truncated set of 12 studies was not remotely representative of the larger scientific literature on the psychological effects of solitary confinement.

B. Overreliance on the Colorado Study

Even "the most thorough sampling and complete data recovery cannot make up for basic limitations in the data base" (Strube, Gardner, and Hartmann 1985, p. 68). Indeed, "An experiment that is deficient in either statistical conclusion validity, internal validity, or construct validity is meaningless and, therefore, worthless. Consequently, it should not be used" (Chow 1987, p. 266). Notwithstanding these basic methodological truisms, tables 2 and 4 in Morgan et al. (2016) reveal that both meta-analyses relied primarily on the fatally flawed Colorado study. It provided the bulk of the effect sizes on which their overall conclusions were based.

Thus, in the first meta-analysis, I counted 24 of 50 relevant effect sizes on "psychological outcomes" that came from the Colorado study. In the second meta-analysis, 140 of 210 effect sizes came from the Colorado study.[19] Because of its sample size, the weights given to the multiple effect sizes from the Colorado study dwarf those of most of the other studies included.

As tables 2 and 4 in Morgan et al. (2016) make clear, they repackaged the Colorado results in a way that allowed them to dominate the analyses.[20] Thus, when they claimed that their results "are even more compelling when one considers that primary studies with the strongest designs produced much smaller effects," they were referring primarily to the un-

[18] The first (Morgan et al. 2016, table 2) included six studies that explicitly addressed psychological effects of solitary confinement: Ecclestone, Gendreau, and Knox (1974), Suedfeld et al. (1982), Miller and Young (1997), Zinger, Wichmann, and Andrews (2001), Andersen et al. (2003), and O'Keefe et al. (2010). The second (Morgan et al. 2016, table 4) added six studies: Walters, Callagan, and Newman (1963), Miller (1994), Coid et al. (2003), Cloyes et al. (2006), and Kaba et al. (2014); but it omitted Suedfeld et al. (1982) and Andersen et al. (2003).

[19] "Anti-social indicators" such as "re-admission" and "behavior" like re-arrest and "physical health" outcomes were omitted from this calculation of psychological effects.

[20] Zinger, Wichmann, and Andrews (2001) accounted for another four effect sizes in table 2 and 30 in table 4. It too is fundamentally flawed, as I explain in the next section. By my count, it and the Colorado study account for 28 of 50 relevant effect sizes in the first meta-analysis and 170 of 210 in the second.

interpretable O'Keefe et al. (2010) study. However, few if any of the fundamental defects of the Colorado study were even mentioned and none was seriously engaged. Instead, the authors simply described the Colorado study as "the most sophisticated study" ever done on the topic (Morgan et al. 2016, p. 441) and relied on it for the bulk of their conclusions.[21]

C. Including Other Methodologically Flawed Studies

There are serious problems with a number of the other studies included in the Morgan et al. (2016) analyses. For example, Zinger, Wichmann, and Andrews (2001) accounted for the next-largest number of effect sizes in their meta-analyses. However, there are several problems with how the results of this study were treated and serious issues with how the study itself was conducted, raising questions about whether it should have been included at all. Its sample size is erroneously listed in table 2 as 136. Although 136 was the initial number of participants, only 60 remained at the end of 60 days. The *N* shown in table 4 is, correctly, the 60 who remained, but that also is misleading. That number includes a majority of prisoners in the "administrative segregation" group (13 of 23) who were there voluntarily. Only 10 involuntary prisoners remained in administrative segregation at the end of 60 days. Thus this study was weighted far too heavily in the first meta-analysis and given a misleading weight in the second.

The results of Zinger, Wichmann, and Andrews (2001) are in any case impossible to interpret. They are based on data from a sample that combined "voluntarily" and "involuntarily" segregated prisoners. Voluntarily isolated prisoners (such as protective custody prisoners who "choose" to be in isolation) control their own fates; at least in theory, they can leave. In addition, in most cases they know that by staying they are at least safe from threats to their well-being elsewhere in the prison system, ones they presumably fear and necessarily want to avoid more than the pain and harm they may endure in solitary confinement. They are thus

[21] Morgan et al. (2016) appear to have overweighted the disproportionate number of effect sizes they took from the Colorado study, treating the *N*'s in each group as though their integrity was maintained throughout. However, as I noted, the bulk of the Colorado study participants moved back and forth between groups. Thus the "uncontaminated" cases are far fewer than Morgan et al. cited and used. Because O'Keefe et al. (2010) did not disaggregate their data, Morgan et al. must have relied on the confounded results, treating all participants as if they remained in their original groups for the duration of the study and weighted effect sizes as if this had been the case.

motivated to adapt to their isolation—or to appear to have adapted to it—in ways that involuntarily isolated prisoners are not. They should not be treated as if their experiences represent the effects of solitary confinement on involuntarily segregated prisoners.

A second and more important problem is the significant amount of attrition that occurred. Especially in longitudinal research, participants leave studies for various reasons. This inevitably complicates comparisons over time or between groups because people who remain are likely to be different from those who leave, thereby changing the compositions of the groups in ways that are difficult to specify.[22] This is especially a problem in prison research because prison administrators decide where prisoners are housed, under what conditions, and for how long; they do so on the basis of considerations that have nothing to do with the goals of researchers. In Zinger, Wichmann, and Andrews (2001), the reduction in the number of administrative segregation prisoners after 60 days, from 83 to 23, only 10 of whom were involuntary, means that attrition reduced the number of involuntarily segregated prisoners by 80 percent. The reasons for the attrition were not given.

Attrition is seldom random. That it results largely, if not entirely, from decisions made by prison administrators means that Zinger, Wichmann, and Andrews (2001) wound up with a group that was significantly different, in indeterminate ways, from the group with which they began.[23] They do not report whether and in what ways the prisoners who remained differed from those with whom the study began.[24]

[22] Zinger, Wichmann, and Andrews acknowledge this: "Attrition is a major drawback to psychological research in general. The problem with attrition is especially relevant to the evaluation of the psychological effects of segregation" (2001, p. 56). However, they ignored the extent of this problem in presenting and interpreting their results.

[23] If, for example, disproportionate numbers of transferred prisoners were considered too "vulnerable" to remain in administrative segregation, were reacting especially negatively, or were adjusting poorly and were especially effective at convincing the prison administration to return them to the general prison population, those left behind would be, by definition, those least affected by the experience. Alternatively, if those who remained at the end of 60 days were the most recalcitrant and least compliant, perhaps explaining why the prison administrators were less likely to release them, they may have been especially "difficult" prisoners who were less likely to admit vulnerability or weakness in the assessments they underwent. Or if the voluntary administrative segregation prisoners remaining after 60 days were the least willing or able to return to the general prison population, they may have been unlikely to admit that they were suffering lest this jeopardize their continued safekeeping. Any of these possible scenarios could greatly compromise interpretation of the results, and none of them appear to have been considered.

[24] The assertion that "none of the attrition was attributable to prisoners being incapable of participating in the study because of episodes of delusion or hallucination or suicide at-

An additional methodological problem was acknowledged in passing but not fully discussed, either in the published article or in Zinger's (1998) dissertation, on which it was based. "Practice effects" are a common problem in longitudinal studies because they require repeated administration over time of the same tests or measures. Participants may recall the questions and intentionally or inadvertently try to reproduce the same or similar answers, or lose interest and reply with stock, rote answers, or, if the tests include performance measures, improve (because of practice) each time they take the test. If any of these things occurs, the existence of real changes (especially negative ones) will be masked or minimized.

Zinger (1998) himself recognized that "artifacts of repeated testing" likely played a role in producing apparent improvements in functioning and the lack of signs of deterioration and that practice effects may have accounted for prisoners "report[ing] less problems over time" (p. 93). He also observed that it is well known that "participants lose interest in answering repeatedly to identical questions and tend to report less problems over time" (p. 92).[25] Thus, practice effects may have accounted in large part for the findings of "no change" or "improvement" on the measures used and repeatedly administered.

There are also significant problems with several other studies that were included in the already small group that Morgan et al. (2016) considered. For example, Cloyes et al. (2006) did not compare administrative segregation with nonadministrative segregation at all. Instead, all of the prisoners involved in their study were in solitary confinement. The effect size Morgan et al. reported was the only statistical test of differences between groups that appeared anywhere in Cloyes et al. (2006, p. 772). However, it is a *t*-test of differences in Brief Psychiatric Rating Scale scores between two groups of solitary confinement prisoners—those identified as seriously mentally ill or not, both of which were housed in isolation. Data from this study did not belong in the meta-analysis.

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tempts" (Zinger, Wichmann, and Andrews 2001, p. 71) sets far too high a threshold and does not adequately address the matter. "Episodes of delusion or hallucination or suicide attempts" are hardly the only measures of whether someone is being so adversely affected that he would seek to be transferred elsewhere or, in the opinion of a correctional administrator or mental health staff member, need to be moved.

[25] Zinger, Wichmann, and Andrews (2001) did acknowledge that reports of "better mental health and psychological functioning over time" are "common in studies which rely on studies with repeated measures designs" (p. 74) but then ignored the implications of this for interpretation of results that showed exactly this.

Walters, Callagan, and Newman (1963) arguably does not belong either. It is over 50 years old and, more importantly, the participants were all volunteers. They were not typical of prisoners involuntarily placed in solitary confinement. In addition, the study lasted only 4 days, not long enough to reach a conclusion that the psychological effects of solitary confinement are minimal. The one effect size Morgan et al. (2016) reported, for "anxiety," is .57 with a weight of .726 (table 4, p. 452). Yet the only mention of numerical data for anxiety in Walters, Callagan, and Newman's study was this: "More isolated than non-isolated prisoners reported an increase in anxiety from the pre-test to post-test period (p = .038, Fisher's Exact Probability Test)." It is impossible to calculate an effect size from this statistic.

Another included study, Andersen et al. (2003, table 2), reported only chi-squares and p-values. It is not clear how Morgan et al. (2016) managed to calculate effect sizes from those data.

The decision to include Ecclestone, Gendreau, and Knox (1974) is also questionable. The study is more than 40 years old and, more importantly, included only prisoners who volunteered to spend 10 days in isolation. For previously noted reasons, the experience of volunteers is not comparable to that of involuntary administrative segregation prisoners. In addition, the study used an almost indecipherable measure of psychological functioning—the Repertory Grid Technique—which does not appear to have been used in published prison research before or since.[26] Moreover, half of the initial participants "quit the experiment after two days of solitary confinement" (p. 179), which meant that the assignment of participants was no longer "random," the results suffered from significant attrition bias, and the remaining volunteer participants knew that they could leave whenever they wanted. Notwithstanding these problems, Ecclestone, Gendreau, and Knox concluded that isolated confinement was "not more stressful than normal institutional life" (p. 178). Morgan et al. (2016) included this study in both meta-analyses and singled it out as having one of the stronger research designs (along with Zinger, Wichmann, and Andrews [2001] and O'Keefe et al. [2010]).[27]

[26] Description of the nature and scoring of the Repertory Grid Technique was so complicated that it consumed nearly two full pages of text (Ecclestone, Gendreau, and Knox 1974, pp. 180–81).

[27] The studies deemed to have stronger research designs were identified by name only in Morgan et al.'s (2016) Research Synthesis I, although an estimate of the strength of the designs was also apparently used in Research Synthesis II. Morgan et al. concluded that

In sum, Morgan et al.'s (2016) meta-analyses were based on one fundamentally flawed and uninterpretable study (O'Keefe et al. 2010), another with an attrition rate of 80 percent over a 60-day period (Zinger, Wichmann, and Andrews 2001), two that were four decades old and included only volunteers (Walters, Callagan, and Newman 1963; Ecclestone, Gendreau, and Knox 1974), and one (Cloyes et al. 2006) that could not provide an effect size on the impact of AS.

Few readers are intimately familiar with the solitary confinement literature or willing to invest the effort to read and evaluate each of the studies cited in Morgan et al. (2016). Similarly, few are willing to carefully to examine the hundreds of effect sizes included in the two meta-analyses or are able to make judgments about the propriety of the particular statistical techniques used in the calculations.[28] The presentation of a vast array of numerical data in Morgan et al. gives the impression of an objective representation of equally meaningful effect sizes, but it is not the reality. Their conclusion that solitary confinement has modest or no significant negative psychological effects is not at all what a significant preponderance of the relevant empirical research shows and is at odds with findings

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these studies with "stronger designs" were the ones that showed "less impairment" due to isolated confinement (p. 456). My critical discussion of the individual studies in question shows why.

[28] Morgan et al. (2016) appear to have used statistical methods that require very stringent assumptions and will give misleading results if these assumptions are violated (e.g., Aguinis, Gottfredson, and Wright 2011). Furthermore, the meta-analytic method they used requires a large number of studies to assess these assumptions, and there were not enough studies to assess them. Specifically, they used a random-effects meta-analysis model. This model assumes that the included studies are a random sample from some definable universe of studies. For example, are the prisons represented in Morgan et al.'s meta-analysis a random sample of all US prisons? If not, they cannot claim that their results generalize to this universe. Random-effects meta-analyses also assume that weights and sample sizes are uncorrelated with the effect sizes. If they are correlated, the results will be biased. The correlation between the sample sizes and effect sizes reported in their table 1 indicate that the correlation is about −.5, which could severely bias the results. In a random-effects meta-analysis, both the mean and the variance of the effect sizes in the universe are key parameters that need to be estimated and both require confidence intervals. Morgan et al. reported only the sample estimate of the variance and not the confidence interval. However, the confidence interval for the variance requires a strong assumption of normally distributed effect sizes, and the confidence interval is very sensitive to minor violations of this assumption. A large number of studies are needed to assess the normality assumption—much larger than the number used. Morgan et al. also appear to have used a new and unproven method for combining multiple effect sizes from a single study. This method requires at least a moderate number of studies (10–20, the more the better), more than the separate meta-analyses that were used. Finally, Morgan et al. also used extremely crude and inaccurate methods to approximate effect sizes in studies that did not provide enough information to correctly compute an effect size.

that are consistent across many decades, theoretically coherent, and buttressed by a very large and growing literature on the harmful effects of social isolation in contexts other than prison.

Misleading repackaging of bad data can ripple through the field and produce an echo chamber in which motivated commentators repeat each others' flawed conclusions. Thus O'Keefe (2017, p. 5) recently asserted that "a recent meta-analysis found small to moderate adverse psychological effects resulting from [solitary confinement] that were no greater in magnitude than the overall effects of incarceration. These findings are consistent with our Colorado results." She was referring to the Morgan et al. (2016) meta-analysis, whose conclusions were not only "consistent" with the Colorado results but based largely on them.

IV. Conclusion

These two studies offer several cautionary tales about the fraught nature of prison research, especially on the methodologically challenging and politically charged topic of solitary confinement. The first of these tales is about the potential influence of bad, uninterpretable data on public discourse and correctional policy. Once the results of research that bear the trappings of science enter into public and policy discourse, it is difficult to correct the record, especially when motivated advocates are willing to overlook fatal flaws in the research. Unfortunately, when this transpires, researchers can lose control of the narrative by which their research is described and the manner in which it is applied. For example, O'Keefe has repeatedly and steadfastly defended her Colorado research but has opposed the uses to which others have put it. She was emphatic that she did "not believe in any way and we do not promote the study as something to argue for the case of segregation. . . . My interpretation is that people believe that this study sanctions administrative segregation for mentally ill and non–mentally ill alike. . . . I do not believe that the conclusions lend to that and that is not the intended use of our study" (2013, p. 96).[29] Yet, that is exactly the use to which a number of interested parties have put it.

[29] Two prominent advisory board members, Jeffrey Metzner and Jamie Fellner (2010), published a "post–Colorado study" article that seemed to contravene the study's findings. They conceded that "isolation can be harmful to any prisoner" and noted that the potentially adverse effects of isolation include "anxiety, depression, anger, cognitive disturbances, perceptual distortions, obsessive thoughts, paranoia, and psychosis" (p. 104)—not at all what

The Colorado study is also a stark reminder that attempts to implement conventional experimental or even quasi-experimental research designs in prison environments face a number of often insurmountable obstacles. The ordinary demands of prison operations nearly always doom even the most carefully planned such studies, and certainly anything resembling a traditional experiment. Savvy prison researchers understand that the desire to treat a prison environment as if it were a research laboratory should be resisted. Real people live (and die) in prison, a setting in which the core dynamics between prisoners and staff are governed by forces beyond the researchers' control.

In separate but related ways, both the Colorado study and the Morgan et al. (2016) meta-analyses underscore the pitfalls of allowing the veneer of scientific rigor to substitute for its reality. They also show the limitations of focusing on quantitative outcomes with little or no concern for precisely how and under what conditions data were acquired. The decontextualized and de-individualized approach to data collection that characterized the Colorado study allowed researchers to treat all participants within each of the study groups as if they were the same, when clearly they—and especially their prison experiences—were not. Ignoring the prison context and individual prisoner trajectories helped render the findings incoherent and uninterpretable.

Similarly, Morgan et al. (2016) illustrate the shortcomings of attempting to apply an otherwise useful approach for summarizing quantitative data to environments as complex and variable as prisons (or especially solitary confinement units). Whatever the benefits of reducing empirical results to effect sizes may be, omitting an entire field's best-known and most in-depth works from consideration because most do not lend themselves to meta-analytic reductions means that nuance and context are inevitably ignored. The compromise in "scientific truth" is far too great.

Some critics of meta-analysis argue that "a literature review should *not* be a formalized or standardized one" (Chow 1987, p. 267; emphasis

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the Colorado study claimed. Metzner and Fellner's deep concerns led them to recommend that professional organizations "should actively support practitioners who work for changed segregation policies and they should use their institutional authority to press for a nationwide rethinking of the use of isolation" in the name of their "commitment to ethics and human rights" (p. 107). Zinger has become an eloquent critic of the use of solitary confinement in Canada (e.g., Makin 2013) even though defenders of the practice continue to cite his dissertation research to justify its use.

added). As Chow observed, "It is not the case that narrative reviews lack rigor. To the contrary, rigor is maintained by reviewers of the traditional [narrative] approach when they evaluate the validity of individual studies" (p. 268). Meta-analyses, even when done well, risk compromising the richness of the prison data they seek to summarize.

In any event, the magnitude of what can be and often is lost in the course of the compromises made in the kind of research critically discussed in this essay often goes unrecognized. Amid thousands of data entries and hundreds of effect sizes reported in these two studies, there are few references to the core subjectivity, institutional trajectory, or life outcome of a single individual prisoner confined in an isolation unit. Nor is there acknowledgment that the studies focused on human beings rather than on interchangeable data points.

Martha Nussbaum (1995) noted in a different context that regarding people as "fungible" and denying them their subjectivity are powerful ways to ensure their objectification. Objectivity in prison research is a worthy goal, except when it results in objectification of prisoners and others in the prison environment. Feeley and Simon (1992) observed that the era of mass imprisonment occasioned and was facilitated by the emergence of a "new penology" whose key elements—"statistical prediction, concern with groups, strategies of management"—shifted the focus of the prison enterprise "toward mechanisms of appraising and arranging groups rather than intervening in the lives of individuals" (p. 459). This actuarial approach still defines the modern prison. It should not be made worse and reinforced by scholarship that exacerbates rather than alleviates or exposes these depersonalizing tendencies.

Studying only at a distance, as the research criticized in this essay did, requires precisely that kind of objectifying sacrifice. If John Irwin was right, that the close study of people in general and prisoners in particular uncovers their humanity, and I think he was, then the opposite is also true. Studying prisoners at a distance, without trying fully to understand and adequately to convey the conditions in which they live or to gain an "appreciation of their meaning worlds, motivations, and aspirations" (1987, p. 47), leaves us with little insight into basic truths about them. That includes whether and how much they are adversely affected by near-total deprivation of meaningful sensory and social contact.

The insurmountable methodological flaws of the Colorado study and the fundamental inadequacy of the Morgan et al. (2016) meta-analysis

should preclude policy makers from using either in debates over the proper use of solitary confinement and the nature of its psychological effects.

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EXHIBIT 27

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Psychiatric Effects of Solitary Confinement

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Psychiatric Effects of Solitary Confinement[†]

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TABLE OF CONTENTS

† This article was prepared from a statement given to the Commission on Safety and Abuse in America's Prisons. As the article is an overview of the psychiatric effects of confinement throughout history it is not fully footnoted

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PREFACE

Dr. Grassian is a Board Certified Psychiatrist who was on the faculty of the Harvard Medical School for over twenty-five years. He has had extensive experience in evaluating the psychiatric effects of solitary confinement, and in the course of his professional involvement, has been involved as an expert regarding the psychiatric impact of federal and state segregation and disciplinary units in many settings. His observations and conclusions regarding this issue have been cited in a number of federal court decisions. The following statement is largely a redacted, non-institution and non-inmate specific, version of a declaration which was submitted in September 1993 in *Madrid v. Gomez*.[1] To enhance the readability of this statement, much of the supporting medical literature is described in the appendices to the statement.

I. OVERVIEW

Solitary confinement—that is the confinement of a prisoner alone in a cell for all, or nearly all, of the day with minimal environmental stimulation and minimal opportunity for social interaction—can cause severe psychiatric harm. It has indeed long been known that severe restriction of environmental and social stimulation has a profoundly deleterious effect on mental functioning; this issue has been a major concern for many groups of patients including, for example, patients in intensive care units, spinal patients immobilized by the need for prolonged traction, and patients with impairment of

1. 889 F. Supp. 1146 (N.D. Cal. 1995), *rev'd and remanded*, 150 F.3d 1030 (9th Cir. 1998).

their sensory apparatus (such as eye-patched or hearing-impaired patients). This issue has also been a very significant concern in military situations, polar and submarine expeditions, and in preparations for space travel.

The United States was actually the world leader in introducing prolonged incarceration, and solitary confinement, as a means of dealing with criminal behavior. The "penitentiary system" began in the United States, first in Philadelphia, in the early nineteenth century, a product of a spirit of great social optimism about the possibility of rehabilitation of individuals with socially deviant behavior.[2] The Americans were quite proud of their "penitentiary system" and they invited and encouraged important visitors from abroad to observe them.[3] This system, originally labeled as the "Philadelphia System," involved almost an exclusive reliance upon solitary confinement as a means of incarceration and also became the predominant mode of incarceration, both for post conviction and also for pretrial detainees, in the several European prison systems which emulated the American model.[4]

The results were, in fact, catastrophic. The incidence of mental disturbances among prisoners so detained, and the severity of such disturbances, was so great that the system fell into disfavor and was ultimately abandoned. During this process a major body of clinical literature developed which documented the psychiatric disturbances created by such stringent conditions of confinement.[5]

The paradigmatic psychiatric disturbance was an agitated confusional state which, in more severe cases, had the characteristics of a florid delirium, characterized by severe confusional, paranoid, and hallucinatory features, and also by intense agitation and random, impulsive, often self-directed violence. Such disturbances were often

2. An excellent history of the Philadelphia System is found in NORMAN JOHNSTON ET AL., EASTERN STATE PENITENTIARY: CRUCIBLE OF GOOD INTENTIONS (1994).

3. *See* DAVID ROTHMAN, THE DISCOVERY OF THE ASYLUM 81 (1971); *see also* GUSTAVE DE BEAUMONT & ALEXIS DE TOCQUEVILLE, ON THE PENITENTIARY SYSTEM IN THE UNITED STATES AND ITS APPLICATION IN FRANCE, http://www.law.du.edu/sterling/Content/ALH/Tocqueville_Pen.pdf; CHARLES DICKENS, AMERICAN NOTES AND PICTURES FROM ITALY (Leonee Ormond ed., Everymans Library 1997) (1842).

4. ROTHMAN, *supra* note 3, at 96–101.

5. *See* Appendix D (describing this literature).

observed in individuals who had no prior history of any mental illness. In addition, solitary confinement often resulted in severe exacerbation of a previously existing mental condition. Even among inmates who did not develop overt psychiatric illness as a result of solitary confinement, such confinement almost inevitably imposed significant psychological pain during the period of isolated confinement and often significantly impaired the inmate's capacity to adapt successfully to the broader prison environment.

It is both tragic and highly disturbing that the lessons of the nineteenth century experience with solitary confinement are today being so completely ignored by those responsible for addressing the housing and the mental health needs in the prison setting. For, indeed, the psychiatric harm caused by solitary confinement had become exceedingly apparent well over one hundred years ago. Indeed, by 1890, with *In re Medley*,[6] the United States Supreme Court explicitly recognized the massive psychiatric harm caused by solitary confinement:

> This matter of solitary confinement is not . . . a mere unimportant regulation as to the safe-keeping of the prisoner . . . .
>
> . . . [E]xperience [with the penitentiary system of solitary confinement] demonstrated that there were serious objections to it. A considerable number of the prisoners fell, after even a short confinement, into a semi-fatuous condition, from which it was next to impossible to arouse them, and others became violently insane; others, still, committed suicide; while those who stood the ordeal better were not generally reformed, and in most cases did not recover sufficient mental activity to be of any subsequent service to the community.[7]

The consequences of the Supreme Court's holding were quite dramatic for Mr. Medley. Mr. Medley had been convicted of having murdered his wife. Under the Colorado statute in force at the time of the murder he would have been executed after about one additional

6. 134 U.S. 160 (1890).
7. *Id*. at 167–68.

month of incarceration in the county jail. But in the interim between Mr. Medley's crime and his trial the Colorado legislature had passed a new statute which called for the convicted murderer to be, instead, incarcerated in solitary confinement in the state prison during the month prior to his execution.[8] Unhappily, when the legislature passed the new law it simultaneously rescinded the older law without allowing for a bridging clause which would have allowed for Mr. Medley's sentencing under the older statute.[9]

Mr. Medley appealed his sentencing under the new statute, arguing that punishment under this new law was so substantially more burdensome than punishment under the old law as to render its application to him *ex post facto*.[10] The Supreme Court agreed with him, even though it simultaneously recognized that if Mr. Medley was not sentenced under the new law, he could not be sentenced at all.[11] Despite this, the Court held that this additional punishment of one month of solitary confinement was simply too egregious to ignore; the Court declared Mr. Medley a free man, and ordered his release from prison.[12]

Dramatic concerns about the profound psychiatric effects of solitary confinement have continued into the twentieth century, both in the medical literature and in the news. The alarm raised about the "brain washing" of political prisoners of the Soviet Union and of Communist China—and especially of American prisoners of war during the Korean War—gave rise to a major body of medical and scientific literature concerning the effects of sensory deprivation and social isolation, including a substantial body of experimental research.[13]

This literature, as well as my own observations, has demonstrated that, deprived of a sufficient level of environmental and social stimulation, individuals will soon become incapable of maintaining an adequate state of alertness and attention to the environment.

8. *Id*. at 162–63.
9. *Id*. at 166.
10. *Id*. at 162.
11. *Id*. at 166.
12. *Id*. at 174.
13. THE MANIPULATION OF HUMAN BEHAVIOR 2–3, 35 (Albert D. Biderman & Herbert Zimmer eds., 1961).

Indeed, even a few days of solitary confinement will predictably shift the electroencephalogram (EEG) pattern toward an abnormal pattern characteristic of stupor and delirium.

This fact is not surprising. Most individuals have at one time or another experienced, at least briefly, the effects of intense monotony and inadequate environmental stimulation. After even a relatively brief period of time in such a situation an individual is likely to descend into a mental torpor or "fog," in which alertness, attention, and concentration all become impaired. In such a state, after a time, the individual becomes increasingly incapable of processing external stimuli, and often becomes "hyperresponsive" to such stimulation. For example, a sudden noise or the flashing of a light jars the individual from his stupor and becomes intensely unpleasant. Over time the very absence of stimulation causes whatever stimulation is available to become noxious and irritating. Individuals in such a stupor tend to avoid any stimulation, and withdraw progressively into themselves and their own mental fog.

An adequate state of responsiveness to the environment requires both the ability to achieve and maintain an attentional set and the ability to shift attention. The impairment of alertness and concentration in solitary confinement leads to two related abnormalities: the inability to focus, and the inability to shift attention. The inability to focus (to achieve and maintain attention) is experienced as a kind of dissociative stupor—a mental "fog" in which the individual cannot focus attention, and cannot, for example, grasp or recall when he attempts to read or to think.

The inability to shift attention results in a kind of "tunnel vision" in which the individual's attention becomes stuck, almost always on something intensely unpleasant, and in which he cannot stop thinking about that matter; instead, he becomes obsessively fixated upon it. These obsessional preoccupations are especially troubling. Individuals in solitary confinement easily become preoccupied with some thought, some perceived slight or irritation, some sound or smell coming from a neighboring cell, or, perhaps most commonly, by some bodily sensation. Tortured by it, such individuals are unable to stop dwelling on it. In solitary confinement ordinary stimuli become intensely unpleasant and small irritations become maddening. Individuals in such confinement brood upon normally

unimportant stimuli and minor irritations become the focus of increasing agitation and paranoia. I have examined countless individuals in solitary confinement who have become obsessively preoccupied with some minor, almost imperceptible bodily sensation, a sensation which grows over time into a worry, and finally into an all-consuming, life-threatening illness.

Individuals experiencing such environmental restriction find it difficult to maintain a normal pattern of daytime alertness and nighttime sleep. They often find themselves incapable of resisting their bed during the day—incapable of resisting the paralyzing effect of their stupor—and yet incapable of any restful sleep at night. The lack of meaningful activity is further compounded by the effect of continual exposure to artificial light and diminished opportunity to experience natural daylight. And the individual's difficulty in maintaining a normal day-night sleep cycle is often far worsened by constant intrusions on nighttime dark and quiet, such as steel doors slamming shut, flashlights shining in their face, and so forth.

There are substantial differences in the effects of solitary confinement upon different individuals. Those most severely affected are often individuals with evidence of subtle neurological or attention deficit disorder, or with some other vulnerability. These individuals suffer from states of florid psychotic delirium, marked by severe hallucinatory confusion, disorientation, and even incoherence, and by intense agitation and paranoia. These psychotic disturbances often have a dissociative character, and individuals so affected often do not recall events which occurred during the course of the confusional psychosis. Generally, individuals with more stable personalities and greater ability to modulate their emotional expression and behavior and individuals with stronger cognitive functioning are less severely affected. However, all of these individuals will still experience a degree of stupor, difficulties with thinking and concentration, obsessional thinking, agitation, irritability, and difficulty tolerating external stimuli (especially noxious stimuli).

Moreover, although many of the acute symptoms suffered by these inmates are likely to subside upon termination of solitary confinement, many—including some who did not become overtly psychiatrically ill during their confinement in solitary—will likely suffer permanent harm as a result of such confinement. This harm is

most commonly manifested by a continued intolerance of social interaction, a handicap which often prevents the inmate from successfully readjusting to the broader social environment of general population in prison and, perhaps more significantly, often severely impairs the inmate's capacity to reintegrate into the broader community upon release from imprisonment.

Many inmates housed in such stringent conditions are extremely fearful of acknowledging the psychological harm or stress they are experiencing as a result of such confinement. This reluctance of inmates in solitary confinement is a response to the perception that such confinement is an overt attempt by authorities to "break them down" psychologically, and in my experience, tends to be more severe when the inmate experiences the stringencies of his confinement as being the product of an arbitrary exercise of power, rather than the fair result of an inherently reasonable process. Furthermore, in solitary confinement settings, mental health screening interviews are often conducted at the cell front, rather than in a private setting, and inmates are generally quite reluctant to disclose psychological distress in the context of such an interview since such conversation would inevitably be heard by other inmates in adjacent cells, exposing them to possible stigma and humiliation in front of their fellow inmates.

II. SOLITARY CONFINEMENT CAN CAUSE SEVERE PSYCHIATRIC HARM

A. Solitary Confinement Can Cause a Specific Psychiatric Syndrome

During the course of my involvement as an expert I have had the opportunity to evaluate the psychiatric effects of solitary confinement in well over two hundred prisoners in various state and federal penitentiaries. I have observed that, for many of the inmates so housed, incarceration in solitary caused either severe exacerbation or recurrence of preexisting illness, or the appearance of an acute mental illness in individuals who had previously been free of any such illness.

I became aware of the particular toxicity of solitary confinement when I first had the opportunity to evaluate prisoners in solitary

confinement as a result of my involvement in a class action lawsuit in Massachusetts, which challenged conditions in solitary confinement at the maximum security state penitentiary in Walpole, Massachusetts.[14] The clinical observations I made in the course of my involvement in that lawsuit, coupled with my research into the medical literature concerning this issue, have formed the basis of two articles I have since published on this topic in peer-reviewed journals.[15] My subsequent professional experience has included observations of similar phenomena in many other solitary confinement settings.

When I initially agreed to evaluate the Walpole prisoners I had not yet reviewed the literature on the psychiatric effects of solitary confinement and I was somewhat skeptical; I expected that inmates would feign illness and exaggerate whatever psychiatric symptomatology they suffered. I discovered, however, something very different. Contrary to my expectations, the prisoners appeared to be extremely defensive about the psychiatric problems they were suffering in Special Housing Unit (SHU); they tended to rationalize away their symptoms, avoid talking about them, or deny or distort their existence all in an apparent effort to minimize the significance of their reactions to isolation. Numerous interviews began with statements such as "solitary doesn't bother me" or "some of the guys can't take it—not me," or even with the mention of a symptom and a simultaneous denial of its significance: "As soon as I got in I started cutting my wrists. I figured it was the only way to get out of here."

As these interviews progressed the facile accounts gave way to descriptions of experiences that were very worrisome. For example, one inmate was unable to describe the events of the several days surrounding his wrist-slashing, nor could he describe his thoughts or feelings at the time. Similarly, the prisoner who said he could "take it" eventually came to describe panic, fears of suffocation, and paranoid distortions which he suffered while in isolation. Moreover,

14. Libby v. Comm'r of Corr., 432 N.E.2d 486 (Mass. 1982).

15. *See* Stuart Grassian & Nancy Friedman, *Effects of Sensory Deprivation in Psychiatric Seclusion and Solitary Confinement*, 8 INT'L J.L. & PSYCHIATRY 49 (1986); Stuart Grassian, *Psychopathological Effects of Solitary Confinement*, 140 AM. J. PSYCHIATRY 1450 (1983).

the specific psychiatric symptoms reported were strikingly consistent among the inmates:

1. The Specific Psychiatric Syndrome Associated with Solitary Confinement

a. Hyperresponsivity to External Stimuli: More than half the prisoners reported a progressive inability to tolerate ordinary stimuli. For example, "You get sensitive to noise, the plumbing system. Someone in the tier above me pushes the button on the faucet . . . It's too loud, gets on your nerves. I can't stand it. I start to holler."

b. Perceptual Distortions, Illusions, and Hallucinations: Almost a third of the prisoners described hearing voices, often in whispers and often saying frightening things to them. There were also reports of noises taking on increasing meaning and frightening significance. For example, "I hear noises, can't identify them—starts to sound like sticks beating men, but I'm pretty sure no one is being beaten . . . I'm not sure." These perceptual changes at times became more complex and personalized:

> They come by with four trays; the first has big pancakes. I think I am going to get them. Then someone comes up and gives me tiny ones—they get real small, like silver dollars. I seem to see movements, real fast motions in front of me. Then seems like they are doing things behind your back, can't quite see them. Did someone just hit me? I dwell on it for hours.

c. Panic Attacks: Well over half the inmates interviewed described severe panic attacks while in SHU.

d. Difficulties with Thinking, Concentration, and Memory: Many reported symptoms of difficulty in concentration and memory. One prisoner described his experience, "I can't concentrate, can't read . . . Your mind's narcotized. Sometimes I can't grasp words in my mind that I know. Get stuck, have to think of another word. Memory's going. You feel like you are losing something you might not get back." In some cases this problem was far more severe, leading to acute psychotic, confusional states. One prisoner had slashed his wrists during such a state and his confusion and disorientation had actually been noted in his medical record.

e. Intrusive Obsessional Thoughts: Emergence of Primitive Aggressive Ruminations: Almost half the prisoners reported the emergence of primitive aggressive fantasies of revenge, torture, and mutilation of the prison guards. In each case the fantasies were described as entirely unwelcome, frightening, and uncontrollable. For example, one prisoner recounted

> I try to sleep sixteen hours a day, block out my thoughts; muscles tense, think of torturing and killing the guards; lasts a couple of hours. I can't stop it. Bothers me. Have to keep control. This makes me think I'm flipping my mind . . . I get panicky, thoughts come back—pictured throwing a guard in lime—eats away at his skin, his flesh—torture him—try to block it out, but I can't.

f. Overt Paranoia: Almost half the prisoners interviewed reported paranoid and persecutory fears. Some of these persecutory fears were short of overt psychotic disorganization. For example, one prisoner recalled "sometimes I get paranoid—think they meant something else. Like a remark about Italians. Dwell on it for hours. Get frantic. Like when they push buttons on the sink. Think they did it just to annoy me." In other cases this paranoia deteriorated into overt psychosis:

> Spaced out. Hear singing, people's voices, 'Cut your wrists and go to Bridgewater and the Celtics are playing tonight.' I doubt myself. Is it real? . . . I suspect they are putting drugs in my food, they are putting drugs in my cell . . . The Reverend, the priest, even you, you're all in cahoots in the Scared Straight Program.

g. Problems with Impulse Control: Slightly less than half of the prisoners reported episodes of loss of impulse control with random violence: "I snap off the handle over absolutely nothing. Have torn up mail and pictures, throw things around. Try to control it. Know it only hurts myself." Several of these prisoners reported impulsive self-mutilation; "I cut my wrists many times in isolation. Now it seems crazy. But every time I did it, I wasn't thinking—lost control—cut myself without knowing what I was doing."

2. This Syndrome has the Characteristics of an Acute Organic Brain Syndrome—A Delirium

Clearly, these symptoms were very dramatic. Moreover, they appeared to form a discreet syndrome—that is, a constellation of symptoms occurring together and with a characteristic course over time, thus suggestive of a discreet illness. Moreover, this syndrome was strikingly unique; some of the symptoms described above are found in virtually no other psychiatric illness. The characteristic acute dissociative, confusional psychoses are a rare phenomenon in psychiatry. Similarly, cases of random, impulsive violence in the context of such confusional state is exceedingly rare. But the most unique symptoms in this cluster are the striking and dramatically extensive perceptual disturbances experienced by the isolated person. Indeed, these disturbances are almost pathognomonic of the syndrome, meaning they are symptoms virtually found nowhere else. For example, loss of perceptual constancy (objects becoming larger and smaller, seeming to "melt" or change form, sounds becoming louder and softer, etc.) is very rare and, when found, is far more commonly associated with neurological illness (especially seizure disorders and brain tumors affecting sensory integration areas of the brain) than with primary psychiatric illness.[16]

In addition, functional psychiatric illness very rarely presents with such severe and florid perceptual distortions, illusions, and hallucinations simultaneously affecting multiple perceptual modalities—auditory, visual, olfactory, tactile, and kinesthetic.[17]

Similarly, hyperresponsivity to external stimuli with a dysesthetic (subjectively painful) response to such stimuli, is likewise rare. In fact, it is exceedingly rare; so rare that appearance of this symptom also might suggest an organic brain dysfunction etiology.[18]

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16. When seen in primary psychiatric illness, it is basically only seen in especially severe, insidious, early onset schizophrenia—the kind of schizophrenic illness which has always been thought to clinically "feel" like a fundamentally biological/neurologic disease.

17. In fact, in the more common psychotic illnesses such as schizophrenia and psychotic depression, auditory hallucinations are by far the most common type; visual hallucinations come a distant second; and hallucinations in all other modalities are actually very uncommon. Moreover, combined modality hallucinations (other than the combination of auditory with visual) are exceedingly rare.

18. This symptom is similar, for example, to the experience many people have during a

Thus, the fact that all of these quite unusual symptoms ran together in the same syndrome was itself a clear confirmation of the distinct nature of this syndrome. While this syndrome is strikingly atypical for the functional psychiatric illnesses, it is quite characteristic of an acute organic brain syndrome: delirium, a syndrome characterized by a decreased level of alertness and EEG abnormalities; by the same perceptual and cognitive disturbances, fearfulness, paranoia, and agitation; and random, impulsive, and self-destructive behavior which I observed in the Walpole population.

Moreover, delirium is a syndrome which is known to result from the type of conditions, including restricted environmental stimulation, which are characteristic of solitary confinement. Even the EEG abnormalities characteristic of delirium have been observed in individuals exposed to conditions of sensory deprivation. By now the potentially catastrophic effects of restricted environmental stimulation have been the subject of a voluminous medical literature; annual international symposia are being held on the subject, and the issue has even found its way into the popular media. The literature is summarized in the appendices to this statement.

B. The Historical Experience with Solitary Confinement: The Nineteenth Century Experience

1. The Origin of the American Penitentiary: The Nineteenth Century German Experience

Preindustrial societies had often not made any fundamental distinction between deviant behavior seen as the product of "criminal intent" as opposed to behavior seen as stemming from "mental illness."[19] For such societies, deviant behavior—whatever its origins—was a social evil that was deeply feared and cruelly punished.

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febrile illness of finding any touching of their body exceedingly unpleasant, or the inability of a patient with a headache to tolerate an even ordinary volume of sound, or the inability of some pregnant women to tolerate even ordinary smells without becoming nauseated.

19. ROTHMAN, *supra* note 3, at 4–5, 62–65.

In Colonial America the Salem witch trials were but one example of a continuing tendency to equate "lunacy" with "demonic possession" and, ultimately, with "evil."[20] Deviant behavior was naturally feared and hated; the instinctive response was to punish it cruelly, lock it away, banish it, or kill its perpetrator. Thus, in Colonial America generally, the social response to deviant behavior was relatively simple: the protection of the larger society was paramount, while the distinction between "illness" and "evil" was far less critical. Indeed, the social response to deviance largely stemmed from the severe puritanical belief in innate human evil that deserved violent retaliation such as whipping, pillories, stockades, brandings, and, ultimately, the gallows. At times, when there was a more "humane" response to persons viewed as suffering from lunacy this response consisted simply of keeping the individual caged under lock and key, often for the rest of his life.

But in the early nineteenth century, a surge of great social optimism swept over America, and along with this grew a belief in the possibility of social reform, perhaps an overly optimistic faith in the possibility of rehabilitation of persons whose behavior was deviant.[21] Not coincidentally, this spirit gave rise virtually simultaneously to two great social reform movements in the United States: the development of large mental hospitals and the construction of the first large penitentiaries.

Both of these institutions were founded upon a similar premise—namely, that psychological and social deviance was largely a result of the evils and stresses of "modern society," and both held a fundamental belief that healing would naturally occur if the deviant individual was removed from the evils of the larger society, and thus enabled to know his own true nature.[22]

In the case of the mental hospital this belief gave rise to the concept of a healing, pastoral, therapeutic community.[23] But, in the case of the penitentiary, an additional safeguard was obviously

20. GEORGE IVES, A HISTORY OF PENAL METHODS: CRIMINALS, WITCHES, LUNATICS 58–59, 68–73 (reprint 1970) (1914).
21. ROTHMAN, *supra* note 3, at 57–58, 79.
22. *Id*. at 82.
23. *Id*. at 133.

required: the inmates clearly had to be protected, not only from the evil influences of the broader society, but also from the evil influences of each other.[24] The proper approach thus appeared to be to give each inmate the opportunity to live a life alone, like a penitent monk in his own monastic cell.

Thus, the earliest American penitentiaries were, generally, systems of rigid solitary confinement.[25] Extravagant attention was paid to the design of these institutions, to ensure the absolute and total isolation of the offender from any evil and corrupting influences.[26] The Philadelphia Prison, completed in 1829, was particularly conscientious in this regard:

> The arrangements . . . guaranteed that convicts would avoid all contamination and follow a path to reform. Inmates remained in solitary cells for eating, sleeping, and working . . . . No precaution against contamination was excessive. Officials placed hoods over the head of a new prisoner when marching him to his cell so he would not see or be seen by other inmates.
>
> . . . Thrown upon his own innate sentiments, with no evil example to lead him astray, . . . the criminal would start his rehabilitation. Then, after a period of total isolation, without companions, books, or tools, . . . [h]e would return to the community cured of vice and idleness, to take his place as a responsible citizen.[27]

The American penitentiary, and the Philadelphia System, became world-famous; no important visitor to the United States neglected to tour its penitentiaries and to bring back their principles for emulation in Europe. Some such as Alexis de Tocqueville of France and Nicholas Julius from Prussia came specifically for that purpose.[28] Tocqueville wrote of the utter, "perfect" desolation of the American

24. *Id*. at 83.
25. *Id*.
26. *Id*. at 82–83.
27. *Id*. at 85–86.
28. *Id*. at 81.

penitentiary, of the "profound silence" within its "vast walls," likening it to the silence of death.[29]

2. Psychological Effects of Severe Isolation

The openness with which these institutions were held up to public scrutiny led in time to open concern about the psychological effects of such confinement. During a tour of the United States in 1842, Charles Dickens wrote with pathos of the Philadelphia Prison:

> The system here is rigid, strict, and hopeless solitary confinement. . . . Over the head and face of every prisoner who comes into the melancholy house, a black hood is drawn, and in this dark shroud, . . . he is led to the cell from which he never again comes forth, until his whole term of imprisonment has expired. He is a man buried alive . . . . dead to everything but torturing anxieties and horrible despair.
>
> . . . .
>
> The first man I saw . . . answered . . . always with a strange kind of pause . . . . He gazed about him and in the act of doing so fell into a strange stare as if he had forgotten something.
>
> In another cell was a German, . . . a more dejected, broken-hearted, wretched creature, it would be difficult to imagine. . . .
>
> There was a sailor . . . . [w]hy does he stare at his hands and pick the flesh open, upon the fingers, and raise his eyes for an instant . . . to those bare walls . . . ?[30]

American concern about the effects of rigid solitary confinement began as early as the 1830s.[31] Statistical comparisons began to be made between the Philadelphia system and its chief competitor: the Auburn system prevailing in New York State at the Auburn and Sing-Sing penitentiaries.[32] The latter system also utilized solitary

29. *Id*. at 97.

30. P. Herbert Liederman, *Man Alone: Sensory Deprivation and Behavioral Change*, 8 CORRECTIONAL PSYCHIATRY & J. SOC. THERAPY 64, 66 (1962).

31. ROTHMAN, *supra* note 3, at 87–88.

32. *Id*. at 88.

confinement, but less rigidly; inmates left their cells to work together in workshops and exercise in a common courtyard, although here, too, absolute and strict silence was maintained at all times.[33] Statistical comparisons began to generate evidence that "[i]t was unnatural . . . to leave men in solitary, day after day, year after year; indeed, it was so unnatural that it bred insanity."[34] The Philadelphia Prison system appeared to have a higher incidence not only of insanity but also of physical disease and death than its New York State system counterpart.[35]

Meanwhile, the American system had been emulated in many major European prisons, such as at Halle, Germany.[36] Although the Americans had been the world leaders in instituting rigid solitary confinement in their penitentiary system, German clinicians eventually assumed the task of documenting its demise. Between 1854 and 1909, thirty-seven articles appeared in German scientific journals on the subject of psychotic disturbances among prisoners, summarizing years of work and hundreds of cases. A major review of this literature was published in 1912.[37] A summary and synthesis of this rather large body of work appears as an appendix to this article.[38]

But it should be noted that interest in the problem was not purely academic; psychotic disturbances among prisoners were of such frequency in these prisons that they attracted administrative as well as clinical concern, and great effort was made to explain this disturbing incidence. Thus, the literature covered a variety of issues: speculation, for example, on the "moral degeneracy" of the prison population; comparison of the psychopathology of those who committed "crimes of passion" with those who committed "crimes against property"; or documentation of the incidence of the major diagnostic categories of the time (for example, "circular insanity," "alcoholic psychoses," epilepsy, and general paresis) among the prison population.

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33. *Id*. at 95, 97.
34. *Id*. at 87.
35. *Id*. at 87–88.
36. *See* PAUL NITSCHE & KARL WILMANNS, THE HISTORY OF THE PRISON PSYCHOSES (Francis M. Barnes, Jr. & Bernard Glueck trans., 1912).
37. *See id*.
38. *See* Appendix B.

However, multiple reports based on careful clinical observation suggested that a substantial majority of these prison psychoses were direct reactions to the conditions of imprisonment itself. Gradually, a clinically distinguishable syndrome of acute reactive prison psychoses began to be defined. Different variables were considered in attempting to explain the etiology of these reactive prison psychoses, including long versus short durations of imprisonment, or imprisonment of those already convicted versus imprisonment while awaiting trial. However, the most consistent factor described, reported in over half the total literature, was solitary confinement.

C. The Twentieth Century Experience: Prisoners of War, "Brain Washing," and Experimental Research

1. Prisoners of War and "Brain Washing"

Unfortunately, other than some anecdotal reports, there was little discussion of the psychological effects of solitary confinement in the medical literature during the first half of the twentieth century. Undoubtedly, this was in part a consequence of the disastrous earlier experience with such confinement. As statistical evidence accumulated during the nineteenth century that solitary confinement produced a very disturbing incidence of insanity, physical disease, and death the system fell into disrepute and, with this, it had changed from an open, optimistic experiment in social reform into a hidden, secretive place of punishment and control.

Its devastating psychological impact, however, did not change, a fact which became suddenly and very painfully evident in the 1950s as the American public began hearing the frightening and dramatic reports of "brain washing" of American prisoners of war in Korea—reports that alterations in the sensory environment were being intentionally imposed upon these prisoners in a seemingly Orwellian attempt to profoundly disrupt their psychological equilibrium.[39]

By the 1950s, reports had already appeared of major psychiatric disturbances among survivors of prolonged solitary confinement in

39. Lawrence E. Hinkle, Jr., *The Physiological State of the Interrogation Subject as It Affects Brain Function*, *in* THE MANIPULATION OF HUMAN BEHAVIOR, *supra* note 13, at 35.

war,[40] but during the decade of the Korean War major attention was riveted on the occurrence of these disturbances not only in war but in a variety of other settings as well. In 1956 the Group for the Advancement of Psychiatry (GAP) held a symposium, "Factors Used to Increase the Susceptibility of Individuals to Forceful Indoctrination," to study methods used by the Chinese and Russian Communists to "indoctrinate" and "break the will" of political prisoners and prisoners of war.[41] Dr. Milton Meltzer, former Chief Medical Officer at Alcatraz Federal Penitentiary, contributed his observations of psychiatric disturbances among prisoners exposed to punitive solitary confinement at Alcatraz.[42] These prisoners were rarely confined for periods beyond one week.[43] Despite this, Dr. Meltzer described acute psychotic breakdowns among prisoners so confined; his descriptions closely paralleled the observations at Walpole:

> The motor effects ranged from occasional tense pacing, restlessness and sense of inner tension with noise making, yelling, banging and assaultiveness at one extreme, to a kind of regressed, dissociated, withdrawn, hypnoid and reverie-like state at the other. . . .
>
> . . . [T]he sense of self, the ego and ego boundary phenomena are profoundly affected by the isolation.[44]

In the same symposium Dr. John Lilly of the National Institute of Mental Health noted that despite the importance of other factors which tended to "weaken personalities and make them more susceptible to [forced indoctrination]"—such as semi-starvation, physical pain and injury, and sleep deprivation—social and sensory isolation was still the central pathogenic factor in such confinement.[45]

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40. *See, e.g.*, CHRISTOPHER BURNEY, SOLITARY CONFINEMENT (1952).

41. *See* GROUP FOR THE ADVANCEMENT OF PSYCHIATRY, FACTORS USED TO INCREASE THE SUSCEPTIBILITY OF INDIVIDUALS TO FORCEFUL INDOCTRINATION (1956).

42. *Id*. at 96–103.

43. *Id*. at 98.

44. *Id*.

45. *Id*. at 89.

2. Experimental Research on Sensory Deprivation

An experimental model was therefore designed to study the effect of such sensory deprivation; this research, conducted during the 1950s and early 1960s, primarily at Harvard and McGill University Medical Centers, was in fact funded in large part by the United States government—and especially by the Department of Defense and the Central Intelligence Agency. This research is described in an appendix to this article.[46] Its relevant conclusions can, however, be described relatively briefly:

In these studies subjects were placed in a situation designed for maximum reduction perceptually informative external stimuli (light-proof, sound-proof rooms; cardboard tubes surrounding the arms and hands to reduce proprioceptive and tactile sensation; and so on).[47] The research revealed that characteristic symptoms generally developed in such settings. These symptoms included perceptual distortions and illusions in multiple spheres (visual, auditory, tactile, olfactory); vivid fantasies, often accompanied by strikingly vivid hallucinations in multiple spheres; derealization experiences; and hyperresponsivity to external stimuli. What was also clear, however, was that while some subjects tolerated such experiences well, many did not, and characteristic syndromes were observed, including the above symptoms and cognitive impairment; massive free-floating anxiety; extreme motor restlessness; emergence of primitive aggressive fantasies which were often accompanied by fearful hallucinations; and a decreased capacity to maintain an observing, reality-testing ego function. In some cases an overt psychosis supervened with persecutory delusions and, in other cases, a marked dissociative, catatonic-like stupor (delirium) with mutism developed. EEG recordings confirmed the presence of abnormalities typical of stupor and delirium.

These findings clearly demonstrated that this experimental model did reproduce the findings in the non-experimental situations,

46. *See* Appendix C.

47. *See, e.g.*, CHARLES A. BROWNFIELD, ISOLATION: CLINICAL AND EXPERIMENTAL APPROACHES (1965); SENSORY DEPRIVATION: A SYMPOSIUM HELD AT HARVARD MEDICAL SCHOOL (Philip Solomon et al. eds., 1961) [hereinafter SENSORY DEPRIVATION—HARVARD].

including the findings among prisoners of war held in solitary confinement.

D. Factors Effecting Response to Sensory Restriction and Solitary Confinement

Much of the subsequent research in this area attempted to delineate variables which might explain these differing outcomes. These variables can be divided into two categories: i) differences among various conditions of perceptual deprivation, and ii) differences in preexisting personality functioning among individuals experiencing such conditions.

1. Differing Conditions of Isolation

One of the factors that was commonly cited in the research was the intensity and duration of the sensory deprivation. More severe sensory restriction, the presence of noxious stimulation, and longer duration of the sensory deprivation experience have all been associated with an increased risk of adverse psychiatric consequences.

In my experience, conditions experienced by inmates in various prison solitary confinement settings generally bear some similarities (a cell of roughly fifty to eighty square feet; approximately twenty-two and one-half hours per day locked in the cell; about one hour per day of yard exercise, five out of the seven days each week), in other respects the conditions are fairly variable. For example, some cells have barred doors, which allow better ventilation, sound transmission, and visual connection with the outside environment than do mesh steel doors; solid steel doors are the most restrictive—especially when they are either hinged or slide shut with almost no air gap from the wall. Moreover, administrative conditions regarding the amount and circumstances of visitation, the availability of reading material and television, and so forth are all factors which vary from institution to institution, and even from time to time within a given institution.

2. The Perceived Intent of the Isolation Experience

In addition to the factors described above, another critical factor in determining the effect of isolation appears to be the perceived intent of the isolation. Experimental research has demonstrated that an individual who receives clues which cause him to experience the isolation situation as potentially threatening is far more likely to develop adverse psychiatric reactions to the isolation experience.[48] Conversely, if the subject has reason to believe the situation is likely to be benign he will be far more likely to tolerate or even enjoy it.[49] Among the latter group of subjects who tolerated isolation well, many reported pleasant or at least non-threatening visual imagery, fantasy, and hallucinatory experiences.[50] "His mind may begin to wander, engage in daydreams, slip off into hypnogogic reveries with their attendant vivid pictorial images . . . he may be quietly having sexual or other pleasurable thoughts."[51]

This finding is perhaps not surprising. It appears that sensory restriction produces perceptual disturbances and illusions which are analogous to those produced by hallucinogenic drugs, and clearly, while there are some individuals who could be said to have volunteered to undergo such hallucinatory, psychotic-like experiences it must be almost uniformly terrifying to be forced to undergo an experience similar to that induced by hallucinogenic drugs.

3. Individual Differences in Response

Many studies have demonstrated that there is great variability among individuals in regard to their capacity to tolerate a given condition of sensory restriction. This variability helps to provide further insight into the nature of the toxic effect of such isolation conditions, and provides striking corroboration of the fact that such

48. *See* Nancy A. Wright & David S. Abbey, *Perceptual Deprivation Tolerance and Adequacy of Defenses*, 20 PERCEPTUAL & MOTOR SKILLS 35 (1965).

49. Leo Goldberger, *Experimental Isolation: An Overview*, 122 AM. J. PSYCHIATRY 774, 777 (1966).

50. *Id*.

51. *Id*.

deprivation of environmental stimulation, especially when of prolonged duration, is toxic to brain functioning and causes symptoms characteristic of stupor and delirium.

Generally, individuals with mature, healthy personality functioning and of at least average intelligence are most able to tolerate the regressive pull and perceptual intrusions of such isolation situations. On the other hand, individuals with primitive or psychopathic functioning or borderline cognitive capacities, impulse-ridden individuals, and individuals whose internal emotional life is chaotic or fearful are especially at risk for severe psychopathologic reactions to such isolation.[52]

Moreover, there is clear evidence that, in a situation of restricted environmental stimulation, preexisting central nervous system dysfunction is a major predisposing factor to the development of adverse psychiatric reactions and of overt delirium. For example, in one study of patients suffering visual deprivation following eye surgery (eye-patched patients), those patients with preexisting central nervous system dysfunction were found to be at especially high risk to develop symptoms of delirium.[53] Further, the presence of a preexisting personality disorder or impairment of psychosocial functioning was associated with increased risk of incapacitating fearfulness, paranoia, agitation, and irrational aggression toward staff.[54]

In addition, individuals may at times be exposed to situations which cause impairment of central nervous system functioning. Such situations—especially if they impair the individual's state of alertness (for example, sleep deprivation, abnormal sleep-wake cycles, or the use of sedating medication) will substantially increase the individual's vulnerability to the development of delirium. Delirium among post-surgical patients and the so-called "ICU psychoses" are examples of this phenomenon.[55] One of the characteristic difficulties

52. *See* Appendix C (describing these studies in more detail).

53. Eugene Ziskind, *Isolation Stress in Medical and Mental Illness*, 168 J. AM. MED. ASS'N 1427, 1428 (1958).

54. Hillel Klein & Rafael Moses, *Psychological Reaction to Sensory Deprivation in Patients with Ablatio Retinae*, 24 PSYCHOTHERAPY & PSYCHOSOMATICS 41, 49–51 (1974). A more extensive review of this literature is contained in Appendix A to this declaration.

55. Appendix A discusses this issue in more detail.

experienced by inmates in solitary confinement is abnormal sleep-wake cycles and impaired sleep.

a. Findings at Pelican Bay State Prison

These findings received further corroboration in my observations of inmates at Pelican Bay State Prison, California. In 1991–1992, as part of my participation in *Madrid v. Gomez*—a class-action lawsuit challenging conditions at Pelican Bay State Prison, a new "supermax" facility in California[56]—I evaluated forty-nine inmates housed in the SHU at the institution and prepared a lengthy report to the federal court of my findings.[57] Many of the inmates I evaluated there suffered severe psychiatric disturbances while housed in Pelican Bay SHU, either springing up de novo while so incarcerated or representing a recurrence or severe exacerbation of preexisting illness. Of the forty-nine inmates I evaluated, at least seventeen were actively psychotic and/or acutely suicidal and urgently in need of acute hospital treatment, and twenty-three others suffered serious psychopathological reactions to solitary confinement, including (in several cases) periods of psychotic disorganization.

The clinical data at Pelican Bay also added striking corroboration to the conclusion that the severe and prolonged restriction of environmental stimulation in solitary confinement is toxic to brain functioning. The data demonstrated that the most severe, florid psychiatric illnesses resulting from solitary confinement tend to be suffered by those individuals with preexisting brain dysfunction. As noted before, I have observed a high incidence of preexisting central nervous system dysfunction among the inmates I evaluated in solitary confinement settings. This was also the case at Pelican Bay, and statistical analysis of the Pelican Bay data quite dramatically demonstrated that inmates with such preexisting vulnerability were the most likely to develop overt confusional, agitated, hallucinatory psychoses as a result of SHU confinement.

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56. Madrid v. Gomez, 889 F. Supp. 1146 (N.D. Cal. 1995), *rev'd and remanded*, 150 F.3d 1030 (9th Cir. 1998).

57. Much of the literature review and historical material in the present declaration is taken from my *Madrid* declaration.

b. Attention Deficit and Antisocial Personality Disorders

In addition, research regarding Attention Deficit Hyperactivity Disorder and Antisocial Personality Disorder demonstrated that these conditions are similarly associated with a particular inability to tolerate restricted environmental stimulation. There is increasing evidence that childhood impulsivity and Attention Deficit Hyperactivity Disorder bear some relationship to Antisocial Personality Disorder, in that both are characterized by impulsivity and stimulation-seeking behavior, and both involve biologically based abnormalities in central nervous system functioning. Moreover, the clinical literature demonstrates that individuals with Antisocial Personality Disorder are especially intolerant of restricted environmental stimulation. For example, the psychopathic individual has been characterized as pathologically "stimulation seeking," "impulsive," and "unable to tolerate routine and boredom."[58]

Given the exigencies of conducting clinical observations of inmates in solitary confinement it is not surprising that little systematic attempt has been made to elucidate the underlying psychological characteristics of those most at risk for developing severe psychopathological reactions to such isolation. However, among the clinical reports on Ganser's Syndrome, a related condition, in non-prison populations are several studies of patients in psychiatric hospitals.[59] These patients were, of course, available for extensive psychological assessment and observation, and these reports described the majority of these patients as suffering long-standing hysterical character disorders, having problems with severe impulsivity, childhood truancy, and antisocial behavior patterns.[60]

Thus, the medical literature demonstrates that individuals whose internal emotional life is chaotic and impulse-ridden and individuals with central nervous system dysfunction may be especially prone to

58. Herbert C. Quay, *Psychopathic Personality as Pathological Stimulation-Seeking*, 122 AM. J. PSYCHIATRY 180, 180 (1965). Appendix B contains a more detailed discussion.

59. *See, e.g.*, Merle R. Ingraham & David M. Moriarty, *A Contribution to the Understanding of the Ganser Syndrome*, 8 COMPREHENSIVE PSYCHIATRY 35 (1967); Rupert H. May et al., *The Ganser Syndrome: A Report of Three Cases*, 130 J. NERVOUS & MENTAL DISEASES 331 (1960).

60. May et al., *supra* note 59, at 331–36.

psychopathologic reactions to restricted environmental stimulation in a variety of settings. Yet, among the prison population, it is quite likely that these are the very individuals who are especially prone to committing infractions that result in stricter incarceration, including severe isolation and solitary confinement.

c. *Langley v. Coughlin*[61]

In the late 1980s I interviewed and reviewed the medical records of several dozen inmates confined in maximum security prisons in New York State, including a large group of women incarcerated at the maximum security women's prison for the state of New York at Bedford Hills. During the process of these evaluations it became clear that a very high percentage of these women had a history of serious emotional or organic mental difficulties. Many had severe cognitive limitations, were highly emotionally labile, impulse ridden, and prone to psychotic disorganization. In many cases the infraction which led to their original incarceration was an act which had been committed impulsively and chaotically. Under the stress of imprisonment these inmates became even more unable to conform their behavior to the requirements of their situation.

Inevitably, this resulted in their being sentenced to terms in the SHU, and once in the SHU their subsequent course was often a nightmare. Many became grossly disorganized and psychotic, smearing themselves with feces, mumbling and screaming incoherently all day and night, some even descending to the horror of eating parts of their own bodies.

The resulting lawsuit was ultimately settled by consent decree. The settlement provided injunctive relief as well as monetary damages both for the mentally ill inmates whose emotional condition had deteriorated during their incarceration in the SHU, and also for the non-mentally ill women who had been subjected to the bedlam of mental illness created in their SHU environment. The injunctive relief required the prison to begin to reframe the meaning it gave to

61. There are two companion cases: *Langley v. Coughlin*, 715 F. Supp. 522 (S.D.N.Y. 1989); and *Langley v. Coughlin*, 709 F. Supp. 482 (S.D.N.Y. 1989), *aff'd*, 888 F.2d 252 (2d Cir. 1989).

behavioral disturbances which they had previously responded to by further SHU time.[62] Under the settlement the prison began to actively consider whether such disturbances were the result of organic personality disturbances, affective or impulse disorders, or even of schizophreniform illness. The result of these changes was apparently quite dramatic.

Many of the prisoners who had been in SHU began to be treated in a residential psychiatric unit within the prison. This unit had previously refused to treat such inmates, claiming that their security needs were greater than could be handled. When pressed to provide services as a result of the settlement not only did the unit discover that it was able to provide those services, but moreover discovered that the custodial and security needs of these inmates dramatically decreased when their behavioral disturbances were framed as psychiatric problems rather than as a security issue. Thus, as a result of the settlement of the lawsuit, all parties to the suit benefited—prisoners and the officers of the correctional facility alike. I followed the result of the litigation in my capacity as an expert member of the settlement.

d. Effects on Psychologically More Resilient Inmates: *Baraldini v. Meese*[63] and *Hameed v. Coughlin*[64]

In 1988 in the course of my involvement in *Baraldini v. Meese*, a class-action challenging the confinement of a small group of women in a subterranean security housing unit at the Federal Penitentiary in Lexington, Kentucky, I had the opportunity to interview several women who were in confinement in this facility. These women had been convicted of having committed politically motivated crimes, were all highly educated, and had a history of relatively strong psychological functioning prior to their confinement. None of these women developed the florid confusional psychosis described earlier in this affidavit, yet each of them demonstrated significant

62. *Langley*, 709 F. Supp. 482.

63. 691 F. Supp. 432 (D.D.C. 1988), *rev'd sub nom*., Baraldini v. Thornburgh, 884 F.2d 615 (D.C. Cir. 1989).

64. 57 F.3d 217 (2d Cir. 1995).

psychopathological reactions to their prolonged confinement in a setting of severe environmental and social isolation. These included perceptual disturbances, free-floating anxiety, and panic attacks. These inmates also uniformly described severe difficulties in thinking, concentration, and memory; for example, one inmate reported that she was able to perform tasks requiring some mental effort—such as reading or writing—only for about the first three hours of the morning after she awoke; by then, her mind had become so slowed down, so much "in a fog," that she was entirely unable to maintain any meaningful attention or expend any meaningful mental effort.

I have since evaluated a number of individuals who evidenced strong psychological adjustment prior to imprisonment. For example, in 1993 I evaluated Bashir Hameed, an inmate who had been incarcerated in the SHU at Shawangunk Correctional Facility and who had brought suit concerning his incarceration there. As I described in my testimony in that case, Mr. Hameed is an individual who evidences strong prior psychological adjustment and no prior psychiatric history, yet became significantly ill as a result of his SHU confinement.

E. Long Term Effects of Solitary and Small Group Confinement

Long-term studies of veterans of prisoner of war camps, and of kidnapping and hostage situations have demonstrated that while many of the acute symptoms I outlined above tend to subside after release from confinement, there are also long-term effects which may persist for decades.[65] These not only include persistent symptoms of post traumatic stress (such as flashbacks, chronic hypervigilance, and a pervasive sense of hopelessness), but also lasting personality changes—especially including a continuing pattern of intolerance of social interaction, leaving the individual socially impoverished and withdrawn, subtly angry and fearful when forced into social interaction.[66]

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65. *See* LAWRENCE E. HINKLE, JR. & HAROLD G. WOLFF, COMMUNIST INTERROGATION AND INDOCTRINATION OF "ENEMIES OF THE STATES" (1956).

66. This literature is reviewed in Appendix D to this declaration.

In addition, from time to time I have had the opportunity to evaluate individuals who had been incarcerated in solitary confinement several years previously. I have found the same pattern of personality change described above: these individuals had become strikingly socially impoverished and experienced intense irritation with social interaction, patterns dramatically different from their functioning prior to solitary confinement.

III. CONCLUSIONS

The restriction of environmental stimulation and social isolation associated with confinement in solitary are strikingly toxic to mental functioning, producing a stuporous condition associated with perceptual and cognitive impairment and affective disturbances. In more severe cases, inmates so confined have developed florid delirium—a confusional psychosis with intense agitation, fearfulness, and disorganization. But even those inmate who are more psychologically resilient inevitably suffer severe psychological pain as a result of such confinement, especially when the confinement is prolonged, and especially when the individual experiences this confinement as being the product of an arbitrary exercise of power and intimidation. Moreover, the harm caused by such confinement may result in prolonged or permanent psychiatric disability, including impairments which may seriously reduce the inmate's capacity to reintegrate into the broader community upon release from prison.

Many of the prisoners who are housed in long-term solitary confinement are undoubtedly a danger to the community and a danger to the corrections officers charged with their custody. But for many they are a danger not because they are coldly ruthless, but because they are volatile, impulse-ridden, and internally disorganized.

As noted earlier in this statement, modern societies made a fundamental moral division between socially deviant behavior that was seen as a product of evil intent, and such behavior that was seen as a product of illness. Yet this bifurcation has never been as simple as might at first glance appear. Socially deviant behavior can in fact be described along a spectrum of intent. At one end are those whose behavior is entirely "instrumental"—ruthless, carefully planned, and

rational; at the other are individuals whose socially deviant behavior is the product of unchecked emotional impulse, internal chaos, and often of psychiatric or neurological illness.

It is a great irony that as one passes through the levels of incarceration—from the minimum to the moderate to the maximum security institutions, and then to the solitary confinement section of these institutions—one does not pass deeper and deeper into a subpopulation of the most ruthlessly calculating criminals. Instead, ironically and tragically, one comes full circle back to those who are emotionally fragile and, often, severely mentally ill. The laws and practices that have established and perpetuated this tragedy deeply offend any sense of common human decency.

APPENDIX A:

REPORTS OF PSYCHIATRIC DISTURBANCES IN OTHER CONDITIONS OF RESTRICTED ENVIRONMENTAL STIMULATION

The psychopathologic syndrome which I have described in the body of this article is found in other settings besides isolation in civil prisons. Some of these settings involve small group, rather than solitary isolation, and the studies have demonstrated that isolated groups comprising two individuals may be the most pathogenic of all. These studies also suggest that those individuals with below average intelligence and poor psychosocial adjustment prior to isolation developed more severe psychiatric difficulties during isolation. In some studies, such disturbances persisted at a one year follow-up after reentry.

I. AVIATION

One particular study, by Bennett, has described psychiatric disturbances among pilots of the British Royal Air Force who had been exposed in-flight to periods of restricted auditory and visual stimulation.[67] All of the groups he described became significantly anxious; many suffered full-blown panic attacks, and many experienced unusual sensations which they were very reluctant to describe. The most severely disturbed groups refused to expose themselves further to the isolation conditions of these flights. At all levels of impairment, however, anxiety was common (both panic and free-floating anxiety). Pilots reported anxiety symptoms such as feeling "hot and tense and powerless" and "nervous and afraid."[68] Feelings of derealization, feelings of detachment from reality, and perceptual distortions were described. Some of these perceptual distortions were dangerous—such as having the impression that the aircraft was turning when it was not—and resulted in serious errors in

67. A.M. Hastin Bennett, *Sensory Deprivation in Aviation*, *in* SENSORY DEPRIVATION—HARVARD, *supra* note 47, at 161–73.

68. *Id*. at 164.

judgment like making the aircraft spiral dangerously downward after attempting to "correct" for what was incorrectly perceived as a turning aircraft.

Another study described strikingly similar symptoms among United States Navy pilots exposed to periods of in-flight isolation.[69] Among pilots who flew alone at high altitude (meaning in a situation of monotonous visual and sensory stimulation) and flying with a minimum of pilot activity, over one third experienced frightening feelings of unreality and became severely anxious.[70]

II. SMALL GROUP CONFINEMENT

Many studies—both anecdotal and experimental—have been made of individuals confined together in small groups. Groups thus described have ranged in size from two to approximately sixty individuals, the larger groups include reports of men isolated on a Pacific island, in submarines, and on Antarctic expeditions.[71] The most consistent finding was of dramatically increased levels of hostility, interpersonal conflict, and paranoia.[72] Individuals exposed to such conditions also tend to become irrationally territorial, staking out "areas of exclusive or special use, [and] acting with hostility to trespasses by others."[73]

Confined groups comprising just two individuals may be the most pathogenic of all, associated with especially high rates of mutual paranoia and violent hostility. Admiral Byrd believed it to be extremely unsafe to staff an Antarctic base unit with just two men:

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69. Brant Clark & Ashton Graybiel, *The Break-off Phenomenon*, 28 J. AVIATION MED. 121 (1957).

70. *Id*. at 122.

71. *See* Seward Smith, *Studies of Small Groups in Confinement*, *in* SENSORY DEPRIVATION: FIFTEEN YEARS OF RESEARCH 374–76 (John Peter Zubek ed., 1969) [hereinafter SENSORY DEPRIVATION: FIFTEEN YEARS]. For articles reporting effects in arctic environments, see Jeanette J. Cochrane & S.J.J. Freeman, *Working in Arctic and Sub-Arctic Conditions: Mental Health Issues*, 34 CAN. J. PSYCHIATRY 884 (1989); Eric Gunderson & Paul D. Nelson, *Adaptation of Small Groups to Extreme Environments*, AEROSPACE MED., Dec. 1963, at 1111; Charles S. Mullin & H.J.M. Connery, *Psychological Study at an Antarctic IGY Station*, 10 U.S. ARMED FORCES MED. J. 290 (1959).

72. Smith, *supra* note 71, at 377.

73. *Id*. at 380.

> [I]t doesn't take two men long to find each other out. . . . [T]he time comes . . . when even his [campmate's] unformed thoughts can be anticipated, his pet ideas become a meaningless drool, and the way he blows out a pressure lamp or drops his boots on the floor or eats his food becomes a rasping annoyance. . . . Men who have lived in the Canadian bush know well what happens to trappers paired off this way . . . .
>
> . . . During my first winter at Little America I walked for hours with a man who was on the verge of murder or suicide over imaginary persecutions by another man who had been his devoted friend.[74]

III. POLAR HABITATION

Psychiatric disturbances have been described in Arctic and Antarctic inhabitants (explorers, researchers, and their support staff), spending varying periods in winter isolation. In these regions, winters last for up to nine months with weather conditions so cold (-100°F) that leaving the confines of the indoors is dangerous.[75] Typically, teams of work groups have fewer than fifty members who spend up to two years working in small quarters.[76] Small group isolation conditions at these stations have been compared to life in prisons by at least one researcher: "[T]he isolation imposed by the harsh environment [of the Antarctic] is rarely experienced outside penal conditions."[77]

A review of the literature on the psychological adjustment to Antarctic living described a staff wintering over at a British Antarctic station; those of the staff who adjusted best tended to be socially mature, intelligent, reserved, and trusting individuals.[78] Similarly,

74. *Id*. at 381.

75. Gunderson & Nelson, *supra* note 71, at 1111.

76. *Id*.

77. Robert J. Biersner & Robert Hogan, *Personality Correlates of Adjustment in Isolated Work Groups*, 18 J. RESEARCH IN PERSONALITY 491, 491 (1989).

78. *See* Esther D. Rothblum, *Psychological Factors in the Antarctic*, 124 J. PSYCH. 253 (1990).

French, United States, and Australian studies revealed that intelligence and previous social adjustment predicted a decreased risk for psychiatric disturbance among workers at Antarctic stations.[79] On the other hand, lack of respect for authority and aggression were important markers for poor isolation adjustment.[80]

Similarly, another study correlated outcome measures with psychological testing obtained prior to work station assignment.[81] These researchers found specifically that persons with antisocial and psychotic tendencies were poor risks for efficient functioning in conditions of isolation.[82]

As a result of these disturbing findings among Antarctic workers, systematic efforts have been made to provide psychological screening of potential station employees and to ameliorate the isolation conditions prevailing in such stations.[83] Despite these efforts, significant psychiatric disturbances have continued to be observed.[84] The fact that these individuals were confined in small groups rather than alone was not found to prevent these disturbances; indeed, one of the central pathogenic factors cited in this literature has been the interpersonal tension and hostility generated by small group confinement.[85]

Studies have described a "winter-over syndrome" including progressively worsening depression, hostility, sleep disturbance, impaired cognitive functioning, and paranoia during small group winter confinement in the Antarctic.[86] Strikingly similar findings were reported by the United States Navy Medical Neuropsychiatric Research Unit, which found high incidences of sleep disturbance, depression, anxiety, aggression, somatic complaints, and a

79. *Id.* at 256; *see also* Smith, *supra* note 71, at 393–95.

80. Mullin & Connery, *supra* note 71, at 292.

81. *See* Morgan W. Wright et al., *Personality Factors in the Selection of Civilians for Isolated Northern Stations*, 8 CAN. PSYCHOLOGIST 23 (1967).

82. *Id*. at 29.

83. Cochrane & Freeman, *supra* note 71, at 889.

84. K. Natani & J. Shurley, *Sociopsychological Aspects of a Winter Vigil at South Pole Station*, *in* HUMAN ADAPTABILITY TO ANTARCTIC CONDITIONS 89–114 (Eugene Gunderson ed., Am. Geophysical Union 1974).

85. *See* Biersner & Hogan, *supra* note 77, at 491–96.

86. *See, e.g.*, R. Strange & W. Klein, *Emotional and Social Adjustment of Recent Winter-Over in Isolated Antarctic Stations*, 7 ANTARCTIC BIBLIOGRAPHY 229 (1974).

progressive impoverishment of social relationships as the winter progressed.[87] Psychiatric problems worsened as the length of time in this confinement increased; in one study of a group of Japanese winter-stationed in the Antarctic, periodic psychological testing revealed increasing levels of anxiety and depression as the winter progressed.[88] Similar findings have been described among a group of Americans stationed in the Antarctic.[89]

A review of the literature on the psychological adjustment to Arctic life described a syndrome which parallels the Antarctic literature: sleep disturbances, apathy, irritability, cognitive dysfunction, hallucinations, depression, and anxiety were widely reported as a result of the small group isolation endured by inhabitants.[90] They also reported "depression, irritability, [and] easily provoked anger which may escalate into dramatic and florid acting out and, not surprisingly, a breakdown in relationships with other members of the group. . . . [I]nsomnia, pallor, loss of appetite, loss of interest, psychomotor retardation, paranoidal ideation, [and] nonspecific hallucinations of light flashes and sudden movements [were also experienced]."[91] Even when Arctic workers were adequately preselected by psychological screening, trained, and supported sleep difficulties, apathy, and irritability persisted.

Studies on reintegration into the home environment after Antarctic living found persisting problems and symptoms including sleep disturbances, cognitive slowing, emotional withdrawal, resentment of authority, indecisiveness, and poor communication even one year after reintegration.[92]

Robert J. Biersner and Robert Hogan summarized the findings related to personality variables in the Arctic and Antarctic workers: "Individuals with high needs for novelty and new sensations, . . . who are emotionally unstable, or who are unconcerned with social

87. *See* E.K. Eric Gunderson, *Emotional Symptoms in Extremely Isolated Groups*, 9 ARCHIVES GEN. PSYCHIATRY 362 (1963); Gunderson & Nelson, *supra* note 71, at 1111–15.

88. Rothblum, *supra* note 78, at 253–73.

89. Gunderson & Nelson, *supra* note 71, at 1114.

90. *See* Cochrane & Freeman, *supra* note 71, at 889.

91. *Id*. at 887.

92. Rothblum, *supra* note 78, at 267.

approval seem unsuited for . . . such environments . . . . The opposite [traits are found in] those who adjust well."[93]

IV. EXPLORERS: SOLO VOYAGES

Anecdotal reports of shipwrecked sailors and individuals accomplishing long solo sea voyages have generally described "disturbances in attention and in organization of thought, labile and extreme affect, hallucinations and delusions."[94] Dramatic anecdotal reports have appeared from time to time. Some of these were summarized in a review article by Dr. Philip Solomon, one of the lead scientists in the Harvard Medical School/Boston City Hospital group:

> Christine Ritter in her very sensitive document *A Woman in the Polar Night*, reported that at times she saw a monster . . . [and] experienced depersonalization to the extent that she thought she and her companions were dissolving in moonlight 'as though it were eating us up' . . . The Spitzbergen hunters use the term ran (strangeness) to describe these experiences . . . .[95]

Tales of the sea have provided many accounts of hallucinatory phenomena. John Slocum sailed alone around the world . . . [In the South Atlantic] he suddenly saw a man, who at first he thought to be a pirate, take over the tiller . . . .

Walter Gibson, a soldier in the British Indian Army, was on a ship torpedoed in the Indian Ocean by the Japanese in World War II . . . . [The shipwrecked survivors] reported that "all of us at various stages in that first week became a prey to hallucinations" . . . [As the weeks passed] the feeling of comradeship disappeared and the men began to find themselves "watching our fellows covertly and suspiciously."[96]

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93. Biersner & Hogan, *supra* note 77, at 495.

94. Peter Suedfeld, *Introduction and Historical Background*, *in* SENSORY DEPRIVATION: FIFTEEN YEARS, *supra* note 71, at 7.

95. Philip Solomon et al., *Sensory Deprivation: A Review*, 114 AM. J. PSYCHIATRY 357, 357–58 (1957).

96. *Id.*

Murder, suicide, and cannibalism followed as social controls dissolved.[97]

V. MEDICAL CONDITIONS

A. Eye Patched Patients

Restricted environmental stimulation conditions also occur post-operatively and in certain medical conditions. In a study of one hundred American patients with macular degeneration of the retina, a high percentage of such patients experienced disturbing visual hallucinations.[98] Those patients who were relatively cognitively limited, those who were socially isolated, and those with simultaneous sensory impairment in another modality (for example, hearing-impaired patients) fared worst.[99] But other factors, including the presence of concomitant medical illness, did not appear to affect the incidence of hallucinations.[100]

In an especially relevant study of eye patched patients, it was determined that psychologically well-adjusted patients (as assessed prior to surgery) tended not to develop visual hallucinations during the period when their eyes were patched, whereas those suffering preexisting personality disturbances did tend to develop such hallucinations.[101] Among those patients who did develop hallucinations, almost half developed complex hallucinations involving human figures and with content suggesting serious preoccupations with themes of depression and anxiety.[102] Moreover, among those patients who had both preexisting personality disturbances and difficulty with their premorbid psychosocial adjustment, eye patching produced severe psychiatric symptomatology, including: paranoid thoughts about being poisoned, physically harmed or attacked; psychomotor agitation; interpersonal

97. *Id.*

98. *See* Suzanne Holroyd et al., *Visual Hallucinations in Patients with Macular Degeneration*, 149 AM. J. PSYCHIATRY 1701, 1703 (1992).

99. *Id*. at 1703–04.

100. *Id*.

101. Klein & Moses, *supra* note 54, at 49.

102. *Id*.

aggressiveness; inability to comply with staff directives; fearful visual hallucinations; and incapacitating anxiety.[103] In this most disturbed group, symptoms had not remitted when observed one week after their eye patches were removed.[104]

Other studies have also found patients to suffer from perceptual distortions, thinking disturbances, and mood changes following the visual deprivation that is part of postoperative recovery in eye surgery.[105] Furthermore, it was noted that "[i]n patients with . . . brain damage, there were also delirioid symptoms, *e.g.*, confusion, disorientation, memory impairment, vivid hallucinations [and disorganized] hyperkinetic activity . . . ."[106] Finally, in C. Wesley Jackson's extensive literature review of hospitalized eye patched patients, psychiatric disturbance was commonly found.[107] These patients suffered from unusual emotional, cognitive, and sensory-perceptual disturbances similar to those previously described.

B. Poliomyelitis

Polio patients confined to tank-type respirators have become psychotic as a direct result of such confinement; moreover, they became more ill, with more florid hallucinations and delusions, at night when sensory input was diminished.[108] The same florid hallucinatory, delusional psychosis has been found in other patients similarly confined in tank respirators.[109]

C. Cardiac Patients

Patients with decompensated heart disease are at times placed on very strict bed rest; some of these patients have developed acute

103. *Id*. at 50.
104. *Id*.
105. *See, e.g.*, Eugene Ziskind et al., *Observations on Mental Symptoms in Eye Patched Patients: Hypnagogic Symptoms in Sensory Deprivation*, 116 AM. J. PSYCHIATRY 893 (1960); Ziskind, *supra* note 53.
106. Ziskind et al., *supra* note 105, at 894.
107. *See* C. Wesley Jackson, Jr., *Clinical Sensory Deprivation: A Review of Hospitalized Eye-Surgery Patients*, *in* SENSORY DEPRIVATION: FIFTEEN YEARS, *supra* note 71, at 337–43.
108. Solomon et al., *supra* note 95, at 361.
109. *Id.* at 362.

confusional, paranoid, hallucinatory psychoses, especially at night during periods of decreased sensory input.

Studies of postoperative open heart surgery patients who were bed confined—their visual stimulation restricted to looking up at a white-tiled hospital room ceiling—revealed a high rate of disordered thinking, visual and auditory hallucinations, and disorientation.[110] There is an extremely disturbing incidence of psychosis following open heart surgery, ranging in various studies from 14% to 30%.[111] Upon recovery these patients described their postoperative environment as a major pathogenic factor in producing their psychiatric illness.[112] Perceptual disturbances and emotional liability, as well as paranoia, depression, and obsessive-compulsive reactions to the restrictive postoperative environment have been documented in other studies as well.[113]

D. Hearing-Impaired Individuals

Another condition of restricted environmental stimulation leading to psychiatric disturbance involves the hearing impaired. Studies of the deaf consistently find significantly higher rates of paranoia in these individuals.[114] High rates of paranoia have been reported in both the developmentally hearing impaired as well as those who

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110. *See, e.g.*, N. Egerton & J.H. Kay, *Psychological Disturbances Associated with Open Heart Surgery*, 110 BRIT. J. PSYCHIATRY 433 (1964); Donald S. Kornfeld et al., *Psychiatric Complications of Open-Heart Surgery*, 273 NEW ENG. J. MED. 287 (1965); Herbert R. Lazarus & Jerome H. Hagens, *Prevention of Psychosis Following Open-Heart Surgery*, 124 AM. J. PSYCHIATRY 1190 (1968); Larkin M. Wilson, *Intensive Care Delirium*, 130 ARCHIVES INTERNAL MED. 225 (1972).

111. Robert E. Lee & Patricia A. Ball, *Some Thoughts on the Psychology of the Coronary Care Unit Patient*, 75 AM. J. NURSING 1498, 1501 (1975).

112. Kornfeld et al., *supra* note 110, at 290.

113. *See, e.g.*, Rosemary Ellis, *Unusual Sensory and Thought Disturbances After Cardiac Surgery*, 72 AM. J. NURSING 2021 (1972); Alvin G. Goldstein, *Hallucinatory Experience: A Personal Account*, 85 J. ABNORMAL PSYCHOL. 423 (1976); Linda Reckhow Thomson, *Sensory Deprivation: A Personal Experience*, 73 AM. J. NURSING 266 (1973); Lee & Ball, *supra* note 111.

114. *See, e.g.*, Kenneth Z. Altshuler, *Studies of the Deaf: Relevance to Psychiatric Theory*, 127 AM. J. PSYCHIATRY 1521 (1971); F. Houston & A.B. Royse, *Relationship Between Deafness and Psychotic Illness*, 100 J. MENTAL SCI. 990 (1954).

became deaf in later life. Experimentally induced deafness in psychiatrically unimpaired adults also produced paranoia.[115]

E. Other Medical Patients

Disorientation and delusional psychoses have also been reported among immobilized orthopedic patients and in patients postsurgically bed-confined. Nursing researchers have studied this phenomenon and have concluded that frightening hallucinatory experiences "are probably far more widespread than has been suspected."[116]

VI. OCCUPATIONAL SITUATIONS

Researchers reported in the New England Journal of Medicine on a study of fifty long-distance truck drivers; of these, thirty experienced vivid visual hallucinations and some became disoriented as if in a dream.[117]

VII. ANIMAL STUDIES

As noted in the body of this article, many prisoners confined in solitary become intolerant of normal levels of environmental (especially social) stimulation. These reports receive experimental confirmation in laboratory research on animals. Such research demonstrates that sensory deprivation produces an intolerance to normal levels of environmental stimulation; animals exposed to sensory deprivation conditions became overly aroused—"hyperexcitable"—when exposed to normal levels of environmental stimulation, often resulting in severe behavioral disturbances.[118]

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115. *See* Phil G. Zimbardo et al., *Induced Hearing Deficit Generates Experimental Paranoia*, 212 SCI. 1529, 1529–31 (1981).

116. Florence S. Downs, *Bed Rest and Sensory Disturbances*, 74 AM. J. NURSING 434, 438 (1974).

117. Ross A. McFarland & Ronald C. Moore, *Human Factors in Highway Safety*, 256 NEW ENG. J. MED. 792, 797 (1957).

118. *See* Austin H. Riesen, *Excessive Arousal Effects of Stimulation After Early Sensory Deprivation*, *in* SENSORY DEPRIVATION—HARVARD, *supra* note 47, at 35–36.

One study produced agitation in mice and rats after a few days of isolation, a report which corroborated previous studies with rats.[119] Others have also found isolation-induced aggressive behavior in mice (such as biting attacks).[120] Further, social isolation has been demonstrated to produce profound and lasting psychological effects in primates. Researchers have noted that over four hundred published investigations of the effects of social isolation on primates show such deleterious effects as self-mutilation and disturbances in perception and learning.[121] They found that in adult rhesus monkeys even brief periods of social isolation produce compromised cognitive processing.[122] Others have produced symptoms of depression in rhesus monkeys by confining them for thirty days.[123] They concluded that solitary "confinement produced greater destructive behavioral effects in less time and with fewer individual differences among subjects than did total social isolation, previously [demonstrated to be] the most powerful technique for producing psychopathological behavior among monkey subjects."[124] Induced depression through confinement has been reported in both young and mature monkeys.[125] Finally, isolation-produced fear in dogs has been clearly demonstrated.[126]

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119. *See* T.C. Barnes, *Isolation Stress in Rats and Mice as a Neuropharmacological Test*, 18 FED'N PROC. 365 (1959).

120. Kinzo Matsumoto et al., *Desipramine Enhances Isolation-Induced Aggressive Behavior in Mice*, 39 PHARMACOLOGY BIOCHEMISTRY & BEHAV. 167, 168 (1991).

121. *See* David A. Washburn & Duane M. Rumbaugh, *Impaired Performance from Brief Social Isolation of Rhesus Monkeys*, 105 J. COMP. PSYCHOL. 145 (1991).

122. *Id*. at 145.

123. William T. McKinney et al., *Depression in Primates*, 127 AM. J. PSYCHIATRY 1313, 1316 (1971).

124. *Id*. at 1317.

125. *See* Harry F. Harlow & Steven J. Suomi, *Induced Depression in Monkeys*, 12 BEHAV. BIOLOGY 273 (1974).

126. *See* W.R. Thompson & R. Melzack, *Early Environment*, 194 SCI. AM. 38 (1956).

APPENDIX B:

THE NINETEENTH CENTURY GERMAN EXPERIENCE WITH SOLITARY CONFINEMENT

Between 1854 and 1909 thirty-seven articles appeared in the German medical literature on the subject of psychotic disturbances among prisoners, summarizing years of work and many hundreds of cases. A major review of this literature was published in 1912.[127] Solitary confinement was the single most important factor identified in the etiology of these psychotic illnesses.

Indeed, the first report on the subject of prison psychoses was that of Delbruck, chief physician of the prison at Halle, in which the frequency of mental disturbances was at last so great that it attracted the attention of the authorities.[128] Delbruck's report concluded that prolonged absolute isolation has a very injurious effect on the body and mind and that it seems to predispose inmates to hallucinations and advised the immediate termination of solitary confinement.[129]

In 1863 Gutsch reported on eighty-four cases of psychosis stemming from solitary confinement and described vivid hallucinations and persecutory delusions, apprehensiveness, psychomotor excitation, sudden onset of the syndrome, and rapid recovery upon termination of solitary confinement.[130] Many of these individuals developed "suicidal and maniacal outbreaks."[131]

In 1871, in a report on fifteen cases of acute reactive psychoses, some of which apparently occurred within hours of incarceration in solitary, Reich described hallucinosis and persecutory delusions in addition to severe anxiety leading to motor excitement—"[t]he patient becomes noisy, screams, runs aimlessly about, destroys and ruins everything that comes in his way."[132] He also described an acute confusional state accompanying these symptoms, sudden

127. *See* NITSCHE & WILMANNS, *supra* note 36.
128. *Id*. at 1.
129. *Id*. at 2.
130. *Id*. at 8.
131. *Id*.
132. *Id*. at 31.

cessation of symptoms, recovery, and subsequent amnesia for the events of the psychosis.[133]

In a statistical summary, Knecht reported in 1891 on the diagnostic assessment of 186 inmates at the "insane department" of the prison at Waldheim and concluded that over half of the total inmates in this department were there due to reactive manifestations to solitary confinement.[134] The majority of these inmates became insane within two years of confinement in solitary.[135]

In 1884 Sommer reported on 111 cases describing an acute, reactive, hallucinatory, anxious, confusional state associated with solitary confinement, emphasizing the "excited outbursts" and "vicious assaults" of these patients.[136] His patients' illness began with difficulty in concentration and hyperresponsivity to minor "inexplicable" external stimuli. These "elementary disturbances of the sensorium (i.e., the five senses)" were seen as leading to "elementary hallucinations" which became more numerous, eventually including auditory, visual, and olfactory hallucinations and eventually becoming incorporated with fearful persecutory delusions.[137]

In 1889 Kirn described 129 cases of psychosis among the inmates at the county jail at Freiburg, concluding that in fifty of those cases, "solitary confinement can be definitely considered as the etiological factor, (and these) show a certain characteristic stamp" including persecutory delusions and hallucinations in multiple spheres (auditory, visual olfactory, tactile).[138] He also noted that these symptoms often precipitated at night:

> [T]he patient is suddenly surprised at night by hallucinatory experiences which bring on an anxious excitement. These manifestations become constant from now on, in many cases occurring only at night, in others also in the daytime. Attentive patients not infrequently hear at first a humming and buzzing

133. *Id*. at 32–33.
134. *Id*.
135. *Id*. at 17.
136. *Id*. at 12, 16.
137. *Id*. at 12–16.
138. *Id*. at 21.

> in their ears, unpleasant noises and inarticulate sounds which they cannot understand until finally they hear well differentiated sounds and distinct words and sentences. . . .
>
> . . . The visual hallucinations are very vivid.[139]

In 1888 Moeli contributed a description of "vorbereiden"—also known as "the symptom of approximate answers."[140] Ten years later Ganser contributed to the literature the elucidation of a syndrome which included Moeli's symptom.[141] As Arieti points out, Ganser's Syndrome became well known—indeed, almost a codification of the whole body of literature on the prison psychoses.[142] Ganser provided a comprehensive and well-elucidated synthesis of symptoms, most of which had been previously described elsewhere. The syndrome he described included (in addition to vorbereiden) vivid visual and auditory hallucinations, a distinct clouding of consciousness, sudden cessation of symptoms "as from a dream," and "a more or less complete amnesia for the events during the period of clouded consciousness."[143] Ganser's most original description was of "hysterical stigmata" within the syndrome, including conversion symptoms, especially total analgesia.[144]

Some of the German authors failed to note whether the inmates they were describing were housed in solitary confinement and, unfortunately, Ganser was one of these, stating only that his were prisoners awaiting trial. However, Langard, in 1901, also reporting on observations of accused prisoners awaiting trial, described an acute violent hallucinatory confusion with persecutory delusions and

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139. *Id*. at 23–24.

140. Vorbereiden is a rather remarkable symptom of deranged and confused thought processes in which the individual's response to a question suggests that he grasped the gist of the question, and his answer is clearly relevant to the question, and related to the obvious correct answer, yet it still oddly manages to be incorrect. An example would be: Q: "How many colors are there in the flag of the United States" A: "Four". Q: "What are they?" A: "Yellow".

141. Ganser, Ueber Einen Eigenartigen Hysterischen Dämmerzustand, 30 ARCHIV FÜR PSYCHIATRIE UND NERVENKRAN-KHEITEN [ARCH PSYCH. & NERVENK] 633 (1898) (F.R.G.).

142. AMERICAN HANDBOOK OF PSYCHIATRY 710–12 (Gerald Caplan ed., 2d ed. 1974).

143. *Id*.

144. *Id.*

specifically stated that this syndrome occurred exclusively among those who awaited trial in solitary confinement.[145]

Also in 1901 Raecke similarly reported on prisoners awaiting trial and described the full syndrome described by Ganser, including vorbereiden; he specifically condemned solitary confinement as responsible for the syndrome.[146] He described his cases as beginning with apathy, progressing to "inability to concentrate, a feeling of incapacity to think," and even catatonic features, including negativism, stupor, and mutism.[147]

In another report, written the same year, Skliar reported on sixty case histories of which he identified twenty-one as acute prison psychoses caused by solitary confinement.[148] While vorbereiden was not noted, most of the other symptoms described by Ganser and Raecke were, including massive anxiety and fearful auditory and visual hallucinations; in severe cases, hallucinations of smell, taste, and "general sensation" as well as persecutory delusions, senseless agitation and violence, confusion, and disorientation.[149] The psychosis developed rapidly, at times within hours of incarceration in solitary confinement.[150] Catatonic symptomatology was also noted.[151]

The German literature reported only on prisoners who suffered gross psychotic symptomatology, some of whom were observed in hospitals or "insane departments" of prisons; thus, these reports generally described only syndromal expressions that rose to the level of overt psychosis. The German reports do, however, powerfully demonstrate the existence of a particular, clinically distinguishable psychiatric syndrome associated with solitary confinement. These multiple reports described a syndrome which included:

1. Massive free-floating anxiety.
2. "Disturbances of the Sensorium," including—

145. NITSCHE & WILMANNS, *supra* note 36, at 32.
146. *Id*. at 34.
147. *Id*. at 33–35.
148. *Id*. at 40.
149. *Id*. at 41.
150. *Id*.
151. *Id*.

a. hyperresponsivity to external stimuli; and

b. vivid hallucinations in multiple spheres (including auditory, visual, olfactory, gustatory, and tactile modalities); in some reports, these began as simple "elementary" hallucinations and progressed to complex, formed hallucinations.

3. Persecutory delusions, often incorporating coexistent complex hallucinations.

4. Acute confusional states. In some reports these were seen as beginning with simple inattention and difficulty in concentration. In others, the onset was described as sudden. The confusional state and disorientation was in several reports described as resembling a dissociative, dreamlike state, at times involving features of a catatonic stupor, including negativism and mutism; and, upon recovery, leaving a residual amnesia for the events of the confusional state. Ganser and others observed hysterical conversion symptoms during this confusional state.

5. Vorbereiden: This was an infrequent finding, mostly described in conjunction with a confusional, hallucinatory state.

6. Motor excitement, often associated with sudden, violent destructive outbursts.

7. Characteristic course of the illness:

a. onset was described by some authors as sudden, by others as heralded by a progression beginning with sensory disturbances and/or inattention and difficulty in concentration; and

b. in many cases, rapid subsidence of acute symptoms upon termination of solitary confinement.

The German reports were generally based upon prisoners who had been hospitalized because of their psychotic illness. In contrast, the population reported upon in the Walpole study was not preselected by overt psychiatric status. Despite this, all of the major symptoms

reported by the German clinicians were observed in the Walpole population, except for vorbereiden and hysterical conversion symptoms. In addition, less severe forms of the isolation syndrome were observed in the Walpole population, including:

- Perceptual distortions and loss of perceptual constancy, in some cases without hallucinations.
- Ideas of reference and paranoid ideation short of overt delusions.
- Emergence of primitive aggressive fantasies which remained ego-dystonic and with reality-testing preserved.
- Disturbances of memory and attention short of overt disorientation and confusional state.
- Derealization experiences without massive dissociative regression.

Since Ganser's report has become the twentieth century's clearest memory of a much vaster body of literature, it is also of interest to review the literature describing observations of Ganser's Syndrome in non-prison populations. Several of these reports have been studies of patients in psychiatric hospitals suffering from this syndrome. Since these patients were hospitalized, it was possible to obtain more extensive evaluation and testing of their status. Several reports described a majority of the patients studied as suffering long standing hysterical conversion symptoms; impulsivity, childhood truancy, and antisocial behavior were also commonly described.[152] These findings suggest also that antisocial behavior patterns and psychopathic personality disorder may bear a close relationship to primitive hysterical personality disorder, a relationship which has been described by other authors as well.[153]

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152. *See, e.g.*, Ingraham & Moriarty, *supra* note 59; May et al., *supra* note 59; Milo Tyndel, *Some Aspects of the Ganser State*, 102 J. MENTAL SCI. 324 (1956); Herbert Weiner & Alex Braiman, *The Ganser Syndrome*, 111 AM. J. PSYCHIATRY 767 (1955).

153. *See* ROBERT A. WOODRUFF, JR. ET AL., PSYCHIATRIC DIAGNOSIS (1974).

APPENDIX C:

EXPERIMENTAL RESEARCH ON THE PSYCHIATRIC EFFECT OF PROFOUND SENSORY DEPRIVATION: FACTORS INFLUENCING VULNERABILITY TO PSYCHIATRIC HARM

As noted in the body of this article, laboratory research has demonstrated that experimentally induced sensory deprivation has major psychological effects and can precipitate severe psychiatric illness. Much of the research in this area attempted to delineate factors in addition to the duration and intensity of sensory restriction which might account for these differing outcomes. The factors which have been elucidated include two which are especially relevant to this discussion and may help to explain the particular malignancy of sensory deprivation in solitary confinement: expectation and individual response.

I. THE INFLUENCE OF EXPECTATION

Research has suggested that a subject's reaction to participation in a sensory deprivation experiment could be profoundly manipulated by external cues imposed by the experimenter:

> [These] dramatic effects could be a function of the demand characteristics of the experimental situation. . . .
>
> There is evidence . . . that preparing a subject for probable hallucinations significantly affects the frequency of hallucinations. . . . [S]uch devices as "panic buttons" in experiments are in a sense eloquent "instructions." The use of such a device increases the subject's expectation that something intolerable may occur, and, with it, the likelihood of a bad experience.[154]

154. Martin T. Orne & Karl E. Scheibe, *The Contribution of Nondeprivation Factors in the Production of Sensory Deprivation Effects: The Psychology of the "Panic Button,"* 68 J. ABNORMAL & SOC. PSYCHOL. 3, 4 (1964) (citations omitted).

In the experiment, the researchers exposed two groups of subjects to identical conditions of sensory deprivation. The experimental group's introduction to the experiment included the presence of a medical "Emergency Tray," and instructions about a "Panic Button." As predicted, the experimental group became significantly more symptomatic in measures of cognitive impairment and restlessness, and also more symptomatic in every other measure—including perceptual aberrations, anxiety, and spatial disorientation.[155]

In a related manner, prisoners in solitary confinement generally view such confinement as threatening and punitive, and often as a deliberate attempt to make them "crack up" or "break my spirit." In light of this, it is not surprising that the only recent report suggesting no major ill effect of solitary confinement utilized prisoners who volunteered to spend four days in solitary confinement.[156]

II. INDIVIDUAL DIFFERENCES IN RESPONSE

Several authors have directed attention to the fact that within a given experimental format, massive differences in response can be observed among individual subjects. Often subjects who tolerated the experimental situation well reported pleasant, or at least non-threatening, visual imagery, fantasy, and hallucinatory experiences. The individual's mind may begin to wander, engage in daydreams, slip off into hypnogogic reveries with their attendant vivid pictorial images. The individual may be quietly having sexual and other pleasurable thoughts.[157]

On the other hand,

> Another subject in the same situation may deal with it in quite another manner. He may soon complain of all manner of things: the bed is causing him a backache, his mind is a blank . . . . [He also complains of] intense boredom, tenseness,

155. *Id*. at 3–12.

156. *See* Richard H. Walters et al., *Effects of Solitary Confinement on Prisoners*, 119 AM. J. PSYCHIATRY 771 (1963).

157. Wright et al., *supra* note 81, at 36.

> depressive feelings or of having unpleasant thoughts or picture-like images that disturb him.[158]

In response to these concerns about the incidence of psychopathological reactions to sensory deprivation, an important thrust of the experimentation in this area has been, by prescreening, to select as subjects only those persons demonstrating, by some measure, psychological strength and capacity to tolerate regression. The theoretical premise of such work has been:

> [I]n the sensory deprivation experiments, it is the ego's autonomy from the drives that is predominately involved . . . . Differences in drive-discharge thresholds, phantasy [sic] and daydream capacity, capacity for what [is] . . . termed "regression in the service of the ego" are other theoretically relevant structural dimensions accounting for differences in isolation behavior.[159]

These ideas have been subjected to experimental verification, which has corroborated that some individuals tolerate such isolation better than others. For example, two researchers, using the Rohrshach Test for prescreening, concluded that the Rohrshach manifestations of an individual's defense and control mechanisms appear to be a reliable measure for predicting whether an individual will be effective in controlling the drive-dominated responses that might emerge during the individual's period of reduced sensory stimulation.[160]

Anecdotal reports in a similar vein appear from time to time in the literature. A subject of one study became panicky during sensory deprivation and stated he had been diagnosed "borderline psychotic."[161] Curtis and Zuckerman report on a psychotic paranoid reaction in one subject who suffered delusions for several days afterward, and severe anxiety and depression lasting several weeks;

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158. Leo Goldberger, *Experimental Isolation: An Overview*, 122 AM. J. PSYCHIATRY 774, 777 (1966).

159. *Id*. at 778 (footnotes omitted).

160. Wright et al., *supra* note 81, at 37.

161. Sanford J. Freedman & Milton Greenblatt, *Studies in Human Isolation II: Hallucinations and Other Cognitive Findings*, 11 U.S. ARMED FORCES MED. J. 1479, 1486 (1960).

personality test prescreening had suggested poor adjustment, hostility, lack of insight, and insecurity in interpersonal relationships.[162]

Others prescreened forty-three subjects and identified seven as suffering "personality deviations." Two of these subjects, who were diagnosed as borderline, developed frightening, aggressive fantasies, paranoia, and difficulty in reality testing; one of them prematurely terminated the experiment. Two others were diagnosed as psychopathic; both forced the premature termination of the experiment by disruptive behavior.[163]

Others, using interview techniques and formal psychological test data, studied the effects of two to six days of sensory deprivation on hospitalized psychiatric patients. Among the previously non-psychotic patients they studied, two developed overt paranoid psychoses during the experiment, ultimately necessitating electroshock treatment. These particular individuals appeared to have been unable to tolerate the emergence of aggressive fantasies and images during the sensory deprivation experience.[164]

A. Effects of Sensory Deprivation on Antisocial Personality Disorder

1. Aversive Conditioning

Individuals with psychopathic personality disorder are probably among the least tolerant of sensory deprivation. One researcher has described the essential core of psychopathic pathology as a pathological inability to tolerate restricted environmental stimulation:

> The psychopath is almost universally characterized as [pathologically stimulus seeking and] highly impulsive . . . . He is unable to tolerate routine and boredom. . . . [H]is outbursts frequently appear to be motivated by little more than a need for thrills and excitement. . . .

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162. George C. Curtis & Marvin Zuckerman, *A Psychopathological Reaction Precipitated by Sensory Deprivation*, 125 AM. J. PSYCHIATRY 255, 256 (1968).

163. *See* Henry U. Grunebaum et al., *Sensory Deprivation and Personality*, 116 AM. J. PSYCHIATRY 878 (1960).

164. *See* H. Azima & Fern J. Cramer, *Effects of Partial Perceptual Isolation in Mentally Disturbed Individuals*, 17 DISEASES NERVOUS SYS. 117 (1956).

> It is the impulsivity and lack of even minimal tolerance for sameness which appear to be the primary and distinctive features of the disorder.[165]

He goes on to argue that psychopathic individuals may chronically exist in a state of relative stimulus deprivation: "[H]ighly impulsive, psychopathic behavior [may be seen] in terms of stimulation-seeking pathology. If decreased reactivity and/or rapid adaptation [to environmental stimuli] do produce in these persons an affective state of unpleasantness close to that produced by severe sensory deprivation or monotony in the normal individual . . . ."[166]

He argues that behavioral impulsivity in such individuals may be an effort at coping with this condition of relative sensory deprivation which they experience: "It may be possible . . . to view much of the impulsivity of the psychopath, his need to create excitement and adventure, his thrill-seeking behavior, and his inability to tolerate routine and boredom as a manifestation of an inordinate need for increases or changes in the pattern of stimulation."[167]

A later study, directly comparing psychopathic inmates with non-psychopathic controls, corroborated these findings. The psychopathic inmates scored significantly higher on measures of boredom susceptibility and of impulsivity. The authors concluded that psychopaths are pathologically stimulation seeking and incapable of tolerating isolation conditions.[168]

Others, in a large scale study of criminal offenders suffering from mental illness, noted that the prevalence of severe mental illness is higher among incarcerated offenders than among the general population; and that, compared with non-mentally ill inmates, the mentally ill inmates were more likely to be housed in solitary. Moreover many of these mentally ill inmates suffered from a combination of psychiatric disorders predisposing them to both psychotic breakdown and to extreme impulsivity (often including

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165. Quay, *supra* note 58, at 80.

166. *Id*. at 182.

167. *Id*. at 181.

168. *See* Timothy D. Emmons & Warren W. Webb, *Subjective Correlates to Emotional Responsivity and Stimulation Seeking in Psychopaths, Normals, and Acting-Out Neurotics*, 42 J. CONSULTING & CLINICAL PSYCHOL. 620 (1974).

substance abuse). Such individuals tended to be highly impulsive, lacking in internal controls, and tended to engage in self-abusive and self-destructive behavior in the prison setting, and especially so when housed in solitary.[169]

Many of the inmates placed in solitary confinement are thus likely to be among the least capable of tolerating the experience, and among the most likely to suffer behavioral deterioration as a consequence of such confinement. Solitary confinement has at times been rationalized as being a form of "aversive conditioning," intended to extinguish negative inmate behaviors. Yet this assertion ignores many of the most basic tenets of any behavior modification treatment, and would in any case clearly violate the ethical guidelines governing the use of aversive conditioning:

a. Ethical Considerations

First of all, since aversive conditioning—the use of punishment as a means of inducing behavior change—is inherently suspect ethically and creates an inherent risk of harm, very clear outcome variables have to be articulated and systematically measured over time. As a result of these serial measurements, there must be clear evidence that the undesirable behavior is in fact lessening in frequency and intensity. Such measurement will also identify those patients for whom such aversive conditioning is actually harmful, allowing these individuals to be removed from the aversive treatment protocol. Were such measurements done in the prison setting, staff would inevitably be required to acknowledge the behavioral deterioration which many inmates were suffering as a result of placement in solitary, and in such cases, ethical considerations would have required transferring the inmate out of such confinement.

b. SHU Incarceration is not Aversive Conditioning

SHU incarceration does not meet criteria for aversive conditioning. Indeed, any behavior modification scheme must define and describe very explicitly two variables:

169. Curtis & Zuckerman, *supra* note 162, at 271–72.

(i) The behavior being changed:

Behavior researchers have learned that in order for a subject to benefit from aversive (or any other form of) conditioning, the behavior at issue must be a single, very clearly defined behavior. When multiple behaviors are responded to by the same reinforcer or punishment, learning and behavior change does not occur. Thus, placement in SHU, which is "punishment" for a host of different behaviors, is simply not being used in a manner consistent with an intent of behavior modification; there is inadequate linkage of any specific behavior to this "punishment."

(ii) The "punishment":

Moreover, SHU confinement is quite clearly not "punishment." To be effective, a "punishment" must be very closely linked in time to the targeted behavior, and for learning to occur, there must be repeated opportunities to experience this close link between the target behavior and the punishment. Thus, the "punishment" must be brief and immediate. For example, a mild but painful electric shock or a sudden very loud noise would be ideal punishments in aversive conditioning.

Occasionally "time outs," the brief use of a seclusion room to quickly control disruptive behavior, are used as part of an aversive conditioning program. But when this technique is employed, it is used very quickly and for a very brief period of time—in order for the "time out" to work as a behavior modifier, there must be very clear alternative behaviors which, when manifested, will immediately end the "time out."

For any behavior modification scheme to work then, there must always be an exquisitely close relationship between behavior and response. Indeterminate or prolonged sentencing to solitary simply has nothing to do with aversive conditioning.

APPENDIX D:

REPORTS OF THE LONG-TERM EFFECTS OF SOLITARY CONFINEMENT IN FORMER POLITICAL PRISONERS AND IN PRISONERS OF WAR: SOLITARY CONFINEMENT AS A MEANS OF "BRAIN WASHING" AND "INDOCTRINATING"

Although concerns about the psychiatric effects of solitary confinement among prisoners of war were raised in the medical literature at least as early as post-World War II, this issue reached massive public exposure only after the fearful news of "brain washing" among American prisoners of war in Korea. As is well known, the 1950's were an era of tremendous fear of Communism and of the attempts by communist states to "indoctrinate" people into their ideology. As noted in the body of this article, in the 1950s the United States Department of Defense and the Central Intelligence Agency sponsored a great deal of research on these issues. The results of extensive research done for the Department of Defense were subsequently published.[170] The paper documented interrogation techniques of the Soviet KGB in regard to the incarceration of political prisoners, and the Chinese communists' imprisonment of American prisoners of war in Korea.

The report indicated that the KGB operated detention prisons, many of which were "modern . . . well built and spotlessly clean . . . [with] attached medical facilities and rooms for the care of sick detainees. An exercise yard is a standard facility."[171] Incarceration in these prisons is almost universally in solitary confinement, in a cell approximately ten feet by six feet in size.[172] "An almost invariable feature of the management of any important suspect under detention is a period of total isolation in a detention cell."[173]

This isolation was seen as a central feature of the imprisonment: "The effects upon prisoners of the regimen in the isolation cell are

170. HINKLE & WOLFF, *supra* note 65.
171. *Id*. at 125.
172. *Id*.
173. *Id*. at 126.

striking. . . . A major aspect of this prison experience is isolation. . . . [In the cells] [h]is internal as well as external life is disrupted" and "he develops a predictable group of symptoms, which might almost be called 'disease syndrome.'"[174]

This syndrome develops over time:

> He becomes increasingly anxious and restless, and his sleep is disturbed. . . .
>
> The period of anxiety, hyperactivity, and apparent adjustment to the isolation routine usually continues from one to three weeks. As it continues, the prisoner becomes increasingly dejected and dependent. He gradually gives up all spontaneous activity within his cell and ceases to care about personal appearance and actions. Finally, he sits and stares with a vacant expression, perhaps endlessly twisting a button on his coat. He allows himself to become dirty and disheveled. . . . He goes through the motions of his prison routine automatically, as if he were in a daze. . . . Ultimately he seems to lose many of the restraints of ordinary behavior. He may soil himself. He weeps; he mutters . . . . It usually takes from four to six weeks to produce this phenomenon in a newly imprisoned man.[175]

Addressing the emotional impact on prisoners of such confinement, the report noted that:

> His sleep is disturbed by nightmares. Ultimately he may reach a state of depression in which he ceases to care about his personal appearance and behavior and pays little attention to his surroundings. In this state the prisoner may have illusory experiences. A distant sound in the corridor sounds like someone calling his name. The rattle of a footstep may be interpreted as a key in the lock opening the cell.

174. *Id*. at 127.
175. *Id*. at 128.

> Some prisoners may become delirious and have visual hallucinations.[176]

However, the report also notes that each individual may respond differently: Not all men who first experience total isolation react in precisely this manner. In some, these symptoms are less conspicuous. In others, dejection and utter despondence set in earlier, or later. Still others, and especially those with pre-existing personality disturbances, may become frankly psychotic.[177]

The authors of this report note that the procedures in the Chinese detention camps are somewhat more complex. Prisoners there underwent an initial period of isolation similar to that found in the Soviet prisons.[178] In the second phase, however they were housed in extremely tight quarters within "group cells" comprising approximately eight prisoners.[179] Under the tensions and hostilities created in this environment, brutality of prisoners by other prisoners was almost inevitable and was, according to the authors, apparently an intended result of this "group cell" confinement.[180]

There are many long-term studies of American prisoners of war; unfortunately, the factor of solitary confinement has not generally been separated out in these studies. However, one relatively recent study of Korean prisoners of war described long-term effects including interpersonal withdrawal and suspiciousness, confusion, chronic depression, and apathy toward environmental stimuli. Irritability, restlessness, cognitive impairment, and psychosomatic ailments were extremely common in the group, most of whom had suffered periods of incarceration in solitary confinement at the hands of the Chinese. This report also included a case report of one individual exposed to harsh conditions of solitary confinement for more than sixteen months; thirty years after release, he continued suffering sleep disturbances, nightmares, fearfulness, interpersonal suspicion and withdrawal, severe anxiety, and severe depression. These former prisoners also had psychosomatic ailments including

176. *Id*.
177. *Id*. at 129.
178. *Id*. at 153.
179. *Id*. at 156.
180. *Id*. at 159.

gastrointestinal disturbances, chronic headaches, and obsessive ruminations. They tended to become confused and thus cognitively impaired and were emotionally volatile and explosive.[181]

In former prisoners of war in the Korean conflict, approximately forty years after their release from confinement, solitary confinement was cited as one of the severe stressors in this group. These former prisoners demonstrated persistent anxiety, psychosomatic ailments, suspiciousness, confusion, and depression. They tended to be estranged and detached from social interaction, suffered from obsessional ruminations, and tended to become confused and cognitively impaired, suffering memory and concentration difficulties which affected their cognitive performance on formal testing.[182]

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181. *See* Patricia B. Sutker et al., *Cognitive Deficits and Psychopathology Among Former Prisoners of War and Combat Veterans of the Korean Conflict*, 148 AM. J. PSYCHIATRY 67 (1991).

182. *Id.* at 68.

EXHIBIT 28

INMATE PROPERTY

(REV. 4/1/14)

MATRIX - AUTHORIZED PERSONAL PROPERTY SCHEDULE (APPS)

Facilities may submit requests to be exempted from the personal property items detailed in these schedules. These Exemption Requests are to be submitted to the Chief, Standardized Procedures Unit (SPU). All requests must include rationale and supporting data such as incident reports, physical plant limitations, etc. In the case of an emergency, where the safety of inmates, staff, or other persons are at immediate risk, the requesting institution may immediately act to restrict an item but must notify the SPU. An exemption request shall be submitted to the SPU within five working days of any locally imposed restriction. Exemption requests will be processed through the appropriate Associate Director and then submitted to the Deputy Director, Division of Adult Institutions (DAI) for approval/disapproval.

Inmates may request to have items added to the APPS through their Inmate Advisory Council (IAC). All IAC requests are subject to review by local institutional administration and may be included with any facility Exemption Requests forwarded to the DAI.

TABLE OF CONTENTS

GRANTED EXEMPTION REQUESTS

AVENAL STATE PRISON

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CALIPATRIA STATE PRISON

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.
- Tennis shoes are not permitted.

CALIFORNIA CORRECTIONAL CENTER

- Personal televisions are not permitted at Level I and II Dormitories.

CALIFORNIA CORRECTIONAL INSTITUTION

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CENTRAL CALIFORNIA WOMEN'S FACILITY

No Exemptions

CENTINELA STATE PRISON

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CALIFORNIA INSTITUTION FOR MEN

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CALIFORNIA INSTITUTION FOR WOMEN (CIW)

No Exemptions

CALIFORNIA MEN'S COLONY

West Facility

- Fans, lamps, portable typewriters, battery rechargers, alternating current (AC)/direct current (DC) adapters, television sets, rechargeable batteries, and powdered creamer are excluded.
- Extension cords and hot pots are permitted by Warden's discretion.

East Facility

- 9 foot extension cord, as permitted at Warden's discretion.

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CALIFORNIA MEDICAL FACILITY

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CORCORAN STATE PRISON

Dormitory Facilities

- Fans, televisions, and musical instruments are not permitted in any dormitory housing.

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CALIFORNIA REHABILITATION CENTER

No Exemptions

GRANTED EXEMPTION REQUESTS (continued)

CORRECTIONAL TRAINING FACILITY

All Facilities

- Tweezers, non-metal, plastic only, permitted for PG A, B, C, and U.

CHUCKAWALLA VALLEY STATE PRISON

Dormitory Facilities

- Dormitory housing is excluded from battery rechargers, hot pots, electric AC power lamps, televisions, electric razors, electric typewriters, AC power adapters.

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

DEUEL VOCATIONAL INSTITUTION

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

FOLSOM STATE PRISON

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

HIGH DESERT STATE PRISON

Level IV Facilities

- Disposable razors and manual typewriters are not permitted.
- Clip on fans and lights are not permitted.
- Styrofoam is not permitted.

Administrative Segregation

- Entertainment appliances are not permitted in units with physical plant limitations.

IRONWOOD STATE PRISON

No Exemptions

KERN VALLEY STATE PRISON

Administrative Segregation Unit

- Entertainment appliances are not permitted in units with physical plant limitations.
- AC appliances are not permitted in ASU B1 intake cells (Correctional Clinical Case Management Services).

CALIFORNIA STATE PRISON, LOS ANGELES COUNTY

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

MULE CREEK STATE PRISON

No Exemptions

NORTH KERN STATE PRISON

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

PELICAN BAY STATE PRISON

All Facilities

- Personal toothbrushes are excluded from all facilities, State-issue only.

Level I and Gym Facilities

- AC appliances are not permitted.

Level II Facilities

- Hand held mirrors, nail clippers, disposable razors, ballpoint pens, pencil sharpeners, and fans are not permitted.

Level IV Facilities

- Hand held mirrors, nail clippers, ballpoint pens, and fans are not permitted.

Administrative Segregation Unit

- Entertainment appliances are not permitted in units with physical plant limitations.

GRANTED EXEMPTION REQUESTS (continued)

PLEASANT VALLEY STATE PRISON

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

RICHARD J. DONOVAN CORRECTIONAL FACILITY

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CALIFORNIA STATE PRISON, SACRAMENTO

All Dormitory Facilities

- Fans, televisions, and musical instruments are not permitted in dormitory housing.

Gymnasium Dormitory Facilities

- AC appliances are not permitted in gymnasium dormitories.

CALIFORNIA SUBSTANCE ABUSE TREATMENT FACILITY AND STATE PRISON, CORCORAN

All Facilities

- Pencil sharpeners are not permitted.

Dormitory Facilities

- Televisions operating on AC power are not permitted in dormitories.
- Battery operated televisions are still permitted in dormitories, but must be able to fit into locker.

Level IV Facilities

- Mirrors are not permitted.

SIERRA CONSERVATION CENTER

Level I and II Facilities

- Televisions are not permitted.
- Hot Pots are not permitted in Conservation Camps, Level I and Level II facilities.

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CALIFORNIA STATE PRISON, SOLANO

Level II Dormitories

- New televisions are not permitted. Previously existing televisions shall be permitted to remain until removed through attrition.

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

SAN QUENTIN STATE PRISON

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

SALINAS VALLEY STATE PRISON

Administrative Segregation Unit

- Entertainment appliances are not permitted in units with physical plant limitations.

VALLEY STATE PRISON FOR WOMEN

No Exemptions

WASCO STATE PRISON

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

CALIFORNIA OUT-OF-STATE-FACILITIES (COCF)

Administrative Segregation Units

- Entertainment appliances are not permitted in units with physical plant limitations.

GRANTED EXEMPTION REQUESTS (continued)

COMMUNITY CORRECTIONAL FACILITIES (CCF) – MALE INMATES

- AC appliances are not permitted.
- Battery operated televisions are not permitted.

CONSERVATION CAMPS (FEMALE)

- Immersion heaters and televisions are not permitted.

COMMUNITY CORRECTIONAL FACILITIES (FEMALE)

- All AC appliances, hot pots and warmers, and extension cords, are not permitted.

COMMUNITY PRISONS MOTHER PROGRAM (CPMP), FEMALE REHABILITATIVE COMMUNITY CORRECTIONAL CENTERS (FRCCC):

- Immersion heaters, televisions, antenna, splitters and coaxial cables are not permitted.
- No food or drinks, bowls, tumblers, can openers, storage containers, or umbrellas.
- No clothing pins, combination locks, foot lockers.
- Colored pattern clothing is permitted.

EXHIBIT 29

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

DIEGO ABREGO AREVALO, et al.,

Petitioners-Plaintiffs,

v.

THOMAS DECKER, in his official capacity as Field Office Director, New York City Field Office, U.S. Immigration & Customs Enforcement, et al.,

Respondents-Defendants.

Civil Action No. _____

DECLARATION OF ROBERT M. SAPOLSKY

I, Robert M. Sapolsky, declare under penalty of perjury, pursuant to 28 U.S.C. § 1746, that the following is true and correct to the best of my knowledge:

RELEVANT BACKGROUND AND QUALIFICATIONS

1. I am the John A. and Cynthia Fry Gunn Professor at Stanford University. I hold joint appointments in the departments of Biology, Neurology & Neurological Sciences, and Neurosurgery. I graduated summa cum laude, Phi Beta Kappa, from Harvard University in 1978, with a degree in biological anthropology. I received my Ph.D. in neuroendocrinology at Rockefeller University. I have been a professor at Stanford since 1987, and holder of an endowed chair since 2002. I have received a number of honors and awards for my work, including the MacArthur Fellowship Genius Grant, an Alfred P. Sloan Fellowship, the Klingenstein Fellowship in Neuroscience, and the John P. McGovern Award for Behavioral Science, awarded by the American Association for the Advancement of Science. I also received the National Science Foundation Presidential Young Investigator Award, as well as awards for Young Investigator of the Year from the International Society for Psychoneuroendocrinology, the Society for Neuroscience, and the Biological Psychiatry Society.

2. As a neuroendocrinologist, I have decades of experience working in the area of stress and the body. My work has included studies of humans, non-human primates, rats and mice, and while focusing mostly on the brain, has included work on cancer progression and viral infections. My lab was one of the pioneers in the early 1990s of developing gene therapy in the injured nervous system, and this involved extensive work with, and molecular manipulation of, viral vectors derived from herpes simplex virus, adenovirus, and adeno-associated virus.

3. I have published approximately 470 peer-reviewed publications in science and/or medical journals, and have single-authored six books. My work has been cited more than 140,000 times which, by a recent meta-analysis, places me in the top 0.1% of measures of scientific impact.

4. My C.V. includes a full list of my honors, experience, and publications, and it is attached as Exhibit A.

5. I am not being compensated for my time reviewing materials and preparing this report.

6. During the past four years, I have testified six times as an expert witness in criminal trials involving murder or attempted murder, in evaluating the neuropsychiatric status of the defendant. None of these involved anything related to viral infections. The cases are: *People v. Vladimir Sotelo* (Cal. 2018); *People v. Anicacio Garcia* (Cal. 2019); *People v. Pedro Lopez* (Cal. 2019) (once at trial and again at retrial); *People v. Arent Bradt* (Cal. 2019); and *State v. Darryl Oliver* (Ga. 2020).

STRESS AND HEALTH: A BRIEF OVERVIEW

7. The word "stress" entered the medical and psychological literature (borrowed from engineering) approximately a century ago, and tens of thousands of papers have examined the subject since then. Broadly, a "stressor" can be defined as an external event that throws an organism out of homeostatic balance, and the "stress-response" is the array of physiological adaptations meant to re-establish homeostasis.

8. In its original medical sense, a stressor was conceptualized as a physical challenge to homeostasis, such as a prey species sprinting from a predator, or a hungry predator sprinting after its prey. The field then expanded in a critical way to include the concept of psychological stressors, which involves the activation of the stress-response by the *anticipation* (accurate or otherwise) of a physical challenge to homeostasis. Classic physical stressors are typically short-term in nature, whereas psychological stressors are more likely to be chronic; crucially, when stress is chronic, there are increased risks and severity of disease.

9. Humans are obviously the most psychologically and socially sophisticated species on earth; disease in humans can arise from chronic stress spanning days to decades, and such stress is typically psychosocial in nature. A partial list of diseases that can be caused by or worsened by stress include Type II diabetes, obesity, metabolic syndrome, hypertension, cardiovascular disease, inflammatory bowel disorders, impaired fertility, accelerated brain aging and cellular senescence, and an array of cognitive and psychiatric disorders.[1]

10. Of greatest relevance to this matter, the longest-recognized pathological consequence of chronic stress (since circa 1930) is suppression of the immune system, worsening of the outcome of immune diseases, and triggering of inflammation. Of critical relevance to

[1] *See, e.g.*, Robert Sapolsky et al., *How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions*, 21 Endocrine Reviews 55-89 (2000); Robert Sapolsky, *Why Zebras Don't Get Ulcers: A Guide to Stress, Stress-Related Disease and Coping* (3d. ed. 2004).

COVID-19, this involves impaired immune defenses against viral infection, and compromised function of the lungs.

STRESS IMPAIRS IMMUNE DEFENSES AGAINST VIRAL INFECTIONS

11. An extensive literature demonstrates that stress compromises the ability of the immune system to defend the body against viral infections; such work has included humans, rodents and livestock as study subjects. While there has not been sufficient time to test this with respect to the SARS-CoV-2 virus, this stress effect has been shown for a wide array of classes of viruses. Thus, stress worsens the consequences of infection with herpes simplex virus (HSV),[2] Epstein-Barr virus (EBV),[3] West Nile Virus,[4] influenza virus,[5] human papilloma virus,[6] viral meningitis and viral endocarditis.[7]

12. The links between stress and impaired viral defense have depended on studies of an array of human stressors. These include the stress of various psychiatric and psychological disorders, experimental psychological stressors, low socioeconomic status, being the primary caregiver for a chronically ill patient, or being an astronaut on a prolonged mission. Collectively, these studies have included more than 150,000 human subjects.

13. Though the specific biological pathways vary from condition to condition, mental illnesses such as anxiety, depression, and bipolar disorder will impair immune function and heighten vulnerability to viral infection.

14. Stress has been shown to disrupt anti-viral defenses in laboratory animals as well. Such stressors include social instability, social defeat, social isolation, or exposure to uncontrollable (versus controllable) shocks. The viruses tested have included those listed in paragraph 11 and, in addition, pseudorabies virus,[8] murine encephalomyelitis virus,[9] and bovine HSV.[10]

15. In some studies, impaired viral defenses are demonstrated by showing impairment of specific constituents of the immune system. This involves decreased levels in the blood

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[2] *See, e.g.*, K. Ashcraft et al., *Psychological stress impairs the local CD8+ T cell response to mucosal HSV-1 infection and allows for increased pathogenicity via a glucocorticoid receptor-mediated mechanism*, 33 Psychoneuroendocrinology 951-63 (2008).

[3] *See, e.g.*, R. Glaser et al., *Stress and the memory T-cell response to the Epstein-Barr virus in healthy medical students*, 12 Health Psych. 435 (1993).

[4] *See, e.g.*, D. Ben-Nathan & G. Feuerstein, *The influence of cold or isolation stress on resistance of mice to West Nile virus encephalitis*. Experientia 46, 285-90 (1990).

[5] *See, e.g.*, J. Tian et al., *A single E627K mutation in the PB2 protein of H9N2 avian influenza virus increases virulence by inducing higher glucocorticoids (GCs) level*, 7(6) PLoS ONE e38233 (2012).

[6] *See, e.g.*, C. Fang et al., *Perceived stress is associated with impaired T-cell response to HPV16 in women with cervical dysplasia*, 35 Ann. Behav. MED 87-96 (2008).

[7] *See, e.g.*, H. Song et al., *Stress related disorders and subsequent risk of life threatening infections: population based sibling controlled cohort study*, 367 Brit. Med. J. 15784 (2019).

[8] *See, e.g.*, J. de Groot et al., *A single social defeat transiently suppresses the anti-viral immune response in mice*, 95 J. Neuroimmunol. 143-51 (1999).

[9] *See, e.g.*, Young E et al., *Chronic social stress impairs virus specific adaptive immunity during acute Theiler's virus infection*, 254 J. Neuroimmunol. 254, 19-27 (2013)

[10] *See, e.g.*, P.D. Hodgson, *Effect of stress on viral bacterial synergy in bovine respiratory disease: novel mechanisms to regulate inflammation*, 6(4) Comp. Func. Genomics 244-250 (2005).

and in tissue of key chemical mediators of anti-viral infection, damaging levels of cytokines, impaired generation of antibodies that specifically target the virus in question, and impaired recruitment of immune cells to the tissue that is virally infected.[11]

16. In some studies, stress-induced impairment of viral defenses has been demonstrated with viral outcomes. These include stress-induced increases in viral replication rates, higher viral titers (the concentration of the virus in the body), impaired clearance of virus from infected tissue, more reactivation of latent viruses, and increased epidemiological evidence of life-threatening viral infections in a population.[12]

17. Finally, in some studies, the outcome has been a pathological one. These include demonstrations of stress worsening virally-induced nerve damage, slower healing of HSV-induced lesions, a variety of pathological effects on the lungs (see below), and lower survival rates. For example, one study demonstrated that physical or psychological stressors in mice cause an approximate 50% increase in mortality rates induced by West Nile Virus.[13]

18. Collectively, these studies show that various types of stressors, in various species, worsen the outcome of viral diseases, as measured by immune outcomes, virological outcomes, disease outcomes and survival rates. The evidence also shows that the degree of immunosuppression worsens the more severe and long-lasting the stress has been.

STRESS AND LUNG DISEASES: RELEVANCE TO SARS-COV-2

19. There are two primary ways in which chronic stress will likely leave an individual at significantly higher risk of contracting COVID-19 and at significantly higher risk of serious illness or death if infected. First, as described above, there is the weakening of the immune system's anti-viral capacities, which will leave the body more vulnerable to viral infections and less able to combat them. Second, there is the specific risk caused by inflammation of the lungs and other organs, which I will describe here.

20. The literature reviewed above considers the adverse effects of stress on tissues and organs throughout the body. The core of SARS-CoV-2's ability to sicken and kill arises from it preferentially targeting the lungs; this, of course, is the reason why symptoms of the disease revolve around respiratory distress, and why shortages of ventilators are so devastating. Thus, it is important to focus on the specific issue of what stress does to lungs and respiration, and the pertinence of this to SARS-CoV-2.

21. Study of the impact of stress on disease has been furthered enormously by the appreciation that chronic stress causes inflammation throughout the body, which exacerbates the course of a wide range of diseases.

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[11] *See, e.g.*, C. Welsh et al., *Effects of stress on the immune response to Theiler's virus--implications for virus-induced autoimmunity*, 17 Neuroimmunomodulation 169-72 (2010).
[12] *See, e.g.*, Song, *supra*; M. Elftman et al., *Stress-induced glucocorticoids at the earliest stages of herpes simplex virus-1 infection suppress subsequent antiviral immunity, implicating impaired dendritic cell function*, 184 J. Immunol. 1867-75 (2010).
[13] *See, e.g.*, Ben-Nathan and Feuerstein, *supra*.

22. Crucially, a variety of stressors cause inflammation in the lungs. Stress-induced lung inflammation has been demonstrated in a number of ways through a variety of outcomes. This includes increased presence in the lungs of inflammatory cells and increased release of their chemical messengers, and increased presence of markers of inflammation in exhaled breath (e.g., increased levels of nitric oxide).

23. Moreover, such stress-induced pulmonary inflammation impairs lung function, including increased bronchoconstriction, increased airway impedance (the former term is a measure of how much lung airways are tightened by smooth muscle; the latter describes the extent of resulting disruption of air flow), decreased lung capacity, tidal volume instability and ribcage abdominal asynchrony (the former is a measure of breathing irregularity; the latter is the likely physiological cause of such irregularities). These pro-inflammatory effects of stress occur in the absence of disease. The result is that the lung tissue will be more vulnerable, people will already have more trouble breathing, and the lungs will have more difficulty clearing fluids. In that sense, the effect of stress on the lungs is similar to that of asthma.

24. Stress also worsens the outcome of pulmonary diseases. The textbook example of this is the ability of stress to cause or worsen asthma. A variety of stressors worsen the pathological features of asthma including worsening of asthma-induced bronchoconstriction, airway impedance, airway inflammation, accumulation of inflammatory lung fluid and decreased lung volume.

25. Finally, stress specifically exacerbates features of viral pulmonary diseases. This includes specifically impairing antiviral immune defenses in lung tissue, and increasing the incidence of respiratory viral infections.

26. Collectively, these studies show that even in the absence of disease, stress causes lung inflammation and impairs lung function. This effect will be particularly pronounced as stress rises from moderate to severe levels. Furthermore, stress worsens the outcome of a number of pulmonary disorders (including pneumonia, as with asthma, and for similar physiological reasons), including respiratory viral diseases. This means that people who have experienced chronic stress who contract a respiratory viral disease are significantly more likely to become seriously ill or even die.

27. Because of the novelty of SARS-CoV-2 and the chaos of an ongoing pandemic, there has been little study to date about the effects of stress on anti-viral defenses against SARS-CoV-2 or against coronaviruses in general. This is not unique, as even with certain preexisting physical conditions, our knowledge of the ways in which they increase vulnerability to SARS-CoV-2 is continually evolving. And nonetheless, as to stress, extrapolations can be made with considerable confidence.

28. First, there are considerable genomic, functional and structural similarities across the entire coronavirus family, allowing one to tentatively generalize to SARS-CoV-2.[14]

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[14] *See, e.g.*, Y. Wang et al., *Nsp1 proteins of group I and SARS coronaviruses share structural and functional similarities*, 10 Infection, Genetics and Evolution 919-924 (2010); H. Jayaram et al., *X-Ray structures of the N- and*

29. Second, there are some key similarities between the coronavirus family and the viruses discussed above. For example, the essential viral proteins that are used to fuse to and invade host cells are heavily conserved between coronaviruses and influenza virus.[15] As another example, Epstein Barr Virus and coronaviruses have their pro-inflammatory effects through heavily overlapping mechanisms.[16] As a final example, bats can be primary zoonotic reservoirs for both papilloma viruses and coronaviruses.[17]

30. Third, a study has found that "low levels of $CD3^{+}CD8^{+}$ T cells" are predictors of high mortality rates from COVID-19.[18] These cells help mediate an immune cascade that kills virally-infected cells. Chronic stress can decrease circulating levels of these cells.

31. Fourth, the CDC lists as one of the groups at high risk from COVID-19 people who have had "prolonged use of corticosteroids and other immune weakening medications."[19] Corticosteroids are synthetic versions of the glucocorticoid stress hormones discussed in several of the studies I have cited. These hormones play an important role as a pathway through which chronic stress weakens the immune system.

32. Finally, the CDC includes among its high risk categories for COVID-19 "[p]eople who are immunocompromised" and notes that "[m]any conditions can cause a person to be immunocompromised."[20] It is my professional judgment that high levels of chronic stress would place people in this category.

PLAINTIFFS' HEIGHTENED RISK FROM COVID-19

33. In reaching my assessment in this section, I have reviewed the declaration of Karla Ostolaza, describing the medical histories and current situations of [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

34. Based on a number of factors, including their serious mental health conditions and the highly stressful nature of their current situations, it is my professional judgment based on my decades of work on stress that each of these individuals has experienced and will continue to experience exceptionally high levels of stress.

C-terminal domains of a coronavirus nucleocapsid protein: Implications for nucleocapsid formation, 80 J. Virology 6612-6620 (2006).

[15] *See* P. Chambers et al., *Heptad repeat sequences are located adjacent to hydrophobic regions in several types of virus fusion glycoproteins*, 71 J. General Virology 3075-3080 (1990).

[16] *See, e.g.*, E. Tirotta, *Epstein–Barr virus-induced gene 3 negatively regulates neuroinflammation and T cell activation following coronavirus-induced encephalomyelitis*, 254 J. Neuroimmunology 110-116 (2013).

[17] *See, e.g.*, Tse H. et al., *Identification of a novel bat papillomavirus by metagenomics*, 7(8)PLoS ONE e43986 (2012).

[18] R.-H. Du et al., *Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: A Prospective Cohort Study*, 55(4) European Respiratory Journal (2020), https://erj.ersjournals.com/content/early/2020/04/01/13993003.00524-2020.

[19] Centers for Disease Control and Prevention, *Groups at higher risk for severe illness* (last accessed Apr. 11, 2020), https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html

[20] *Id.*

35. Because of the effects of such high levels of stress on the immune system and the body described above, these individuals are therefore likely at considerably heightened risk of contracting COVID-19 and becoming severely ill and even dying if they do.

CONCLUSIONS

36. An extensive peer-reviewed literature demonstrates that stress compromises antiviral immune defenses and increases viral virulence. These findings are derived from studies of humans and other species, with large sample sizes, examining a variety of stressors and viral insults. Moreover, in the absence of disease, stress causes inflammation in the lungs and impairs respiration. Furthermore, stress specifically exacerbates the consequences of the respiratory viral diseases that are most similar to SARS-CoV-2. This is partly because stress can exacerbate the pulmonary inflammation and buildup of fluid that is central to the pathology of pneumonia. Finally, these effects are of sufficient magnitude that they significantly worsen critical disease outcomes, which include mortality rates. In other words, people who have experienced chronic stress are more likely to die of viral respiratory illnesses.

37. As noted above, there has been insufficient time for the study of stress effects on immune defenses against SARS-CoV-2 and the pathogenic course of COVID-19 specifically. However, given the array of viruses and viral diseases examined in the stress literature, including respiratory diseases that are quite close to COVID-19, and the array of pathophysiological outcomes, I can state with considerable confidence that stress will significantly increase the risk of SARS-CoV-2 infection and markedly worsen the consequences of this infection. This includes a heightened risk of severe illness or even death.

38. It is therefore my professional judgment that people who have suffered from chronic stress are at heightened risk from COVID-19 and fall into the CDC high risk category of "[p]eople who are immunocompromised."[21] Further, given the gravity of this heightened risk, it would be dangerous for both those who have suffered chronic stress and those around them to not treat them as if they were at particularly elevated risk.

39. For these reasons, it is also my professional judgment that [redacted], [redacted], [redacted], [redacted], and [redacted] are at significantly heightened risk from COVID-19.

I declare under penalty of perjury that the foregoing is true and correct.

April 13th, 2020
Palo Alto, California

Robert M. Sapolsky

[21] *Id.*

ROBERT MORRIS SAPOLSKY

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Educational History

l984 Ph.D. Neuroendocrinology, The Rockefeller University
l978 A.B. Biological Anthropology, Harvard University, summa cum laude, Phi Beta Kappa

Professional Experience

2002: John A. and Cynthia Fry Gunn Professor, Department of Biological Sciences, Stanford University; Departments of Neurology and Neurological Sciences, and of Neurosurgery, Stanford University School of Medicine.
l995: Professor
l99l - l995: Associate Professor with tenure
l987 - l99l: Assistant Professor, Department of Biological Sciences, Stanford University
l985: Research Associate, Institute of Primate Research, National Museums of Kenya, Nairobi, Kenya
l985 - l987: Postdoctoral Fellow, Peptide Biology Laboratory, Salk Institute

Professional Awards and Honors

l985: Lindsley Prize of the Society for Neuroscience (outstanding doctoral thesis in behavioral neuroscience).
l987: MacArthur Fellow of the John D. and Catherine T. MacArthur Foundation
Faculty Scholar, Alzheimers Association
Faculty Scholar, Sloan Foundation
Faculty Scholar, Klingenstein Foundation
Presidential Young Investigator, National Science Foundation
l990: A.B. Bennett Award, Society of Biological Psychiatry, young investigator of the year
C. Richter Award, International Society of Psychoneuroendocrinology, young of the year
Winner of Dean's Award for distinguished teaching
l992: Young Investigator of the Year Award, Society for Neuroscience
Research Career Development Award, NIH
Winner of Associated Students of Stanford University Teaching Award
l993: Bing Award for Teaching Excellence
l994: Finalist, Los Angeles Times Book Award for "Why Zebras Don't Get Ulcers"
l996: Elected as Fellow, American Association of the Advancement of Science
l997: Elected as Fellow, California Academy of Sciences
l998: Finalist, Los Angeles Times Book Award for "The Trouble With Testosterone."
Hoagland Prize for Teaching Excellence, Stanford University
2002: "A Primate's Memoir": winner of non-fiction book of the year, Bay Area Book Reviewers Association; finalist, Aventis Prize; finalist, The Natural World Book Prize. Winner of Book of the Year, BILD DER WISSENSCHAFT, German edition.
Winner of "The Emperor Has No Clothes" Award, Freedom From Religion Foundation
2004: Finalist, National Magazine Award, essay division for "The pleasures (and pain) of 'maybe'", Natural History magazine.
Paper # 315 included in Pinker S 2004 The Best American Science and Nature Writing. Houghton Mifflin Co, NY.
2006: Earl Usdin Award of the West Coast College of Biological Psychiatry
2007: John P. McGovern Award, American Association for the Advancement of Science.
2009: Gores Award for Teaching Excellence, Stanford University.
Lewis Thomas Award, Rockefeller University.

Fellow, Association of Psychological Science
2010: Isaac Asimov Award, American Humanist Association
2013: Distinguished Scientific Contributions Award, American Psychological Association
Paper #440 included in Mukherje S 2013 Best American Science and Nature Writing. Mariner Books, NY.
2018: Winner, LA Times Book Prize, Science & Technology
Winner, Phi Beta Kappa Science Book Award
The Against Stupidity award of the Philosophy Now Society, London.
Finalist, PEN Literary Award.

Current and Past Professional Activities

Editorial board: Neurobiology of Aging
Journal of Neuroscience
Psychoneuroendocrinology
Journal of Neurochemistry
Stress
Frontiers in Cultural Psychology

Professional Writing Associations

2012 - Contributing writer to the Opinion column, Los Angeles Times.
2013 - 2017 Bi-weekly columnist, "Mind & Matter" column, Wall Street Journal.

Patents

8,101,158: Methods for treating cerebrovascular disease comprising administering an agent that inhibits prokineticin receptor activity.

College Courses on Video/Audio: The Teaching Company/The Great Courses

Sapolsky R. Biology and Human Behavior: The Neurological Origins of Individuality. 1994; 2005 2nd edition.
Sapolsky R. Stress and Your Body. 2010.
Sapolsky R. Being Human: Life Lessons from the Frontiers of Science. 2012.

Publications: Books

1. Sapolsky R. l992 *Stress, the Aging Brain, and the Mechanisms of Neuron Death*. MIT Press.

2. Sapolsky R. l994 *Why Zebras Don't Get Ulcers: A Guide to Stress, Stress-Related Disease and Coping*. Scientific American/Freeman Press/Henry Holt. Thirteen foreign language editions; Los Angeles Times Book Award finalist. l998: Second edition. 2004: third edition.

3. Sapolsky R l997 *'The Trouble With Testosterone' and Other Essays on the Biology of the Human Predicament*. Simon and Schuster/Scribner, l997; Two foreign language editions; Los Angeles Times Book Award finalist.

4. Sapolsky R 2001 *A Primate's Memoir.* Simon and Schuster/Scribner, nine foreign language editions. Non-fiction book of the year, Bay Area Book Reviewer's Association, 2002; finalist, Aventis Prize; finalist, The Natural World Book Prize.

5. Sapolsky R. 2005 *'Monkeyluv' and Other Essays on our Lives as Animals*. Simon and Schuster/Scribner. Four foreign language editions.

6. Sapolsky R. 2017 *Behave: The Biology of Humans at our Best and Worst*. Penguin/Random House. Nineteen foreign language editions. Winner, LA Times Book Prize; Winner, Phi Beta Kappa Science Book Award; Finalist, 2018 PEN Literary Science Writing Prize.

Publications: Articles and Book Chapters

l. Sapolsky R, H Eichenbaum l980 Thalamo-cortical mechanisms in odor guided behavior. Brain Behavior and Evolution l7, 276.

2. Sapolsky R, H Eichenbaum l980 Still-life photographs: The power of human ethology in the explanation of human behavior. Behavioral and Brain Sciences 3, 628.

3. Sapolsky R l982 The endocrine stress-response and social status in the wild baboon. Hormones and Behavior l5, 279.

4. Sapolsky R, L Krey, B McEwen l983 The adrenocortical stress-response in the aged male rat: Impairment of recovery from stress. Experimental Gerontology l8, 55.

5. Sapolsky R, B McEwen, T Rainbow l983 Quantitative densitometry of steroid hormone receptors. Brain Research 27l, 33l.

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EXHIBIT 30

PSYCHIATRY online

PSYCHIATRIC NEWS

Back to table of contents Previous Article Next Article

CLINICAL & RESEARCH

Patients With SMI in the Age of COVID-19: What Psychiatrists Need to Know

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Psychiatrists taking care of people with serious mental illness need information about changed vulnerabilities and unique treatment requirements of this population during the COVID-19 pandemic, as well as what new or changed resources are available to them.

The tsunami of information on COVID-19 has overwhelmed us all. The advisories, guidelines, and directives have, for the most part, been addressing the population as a whole, as well they should be. Those with disabilities have slid to the sidelines with few attending to what issues they face in this pandemic. In this article we look at a population core to the mission of APA, people with serious mental illness (SMI). We examine COVID-19 issues as they impact both inpatients and outpatients, looking at symptoms, service locations, comorbidities, and medications. In addition, we examine how prejudice against those with SMI is impacted by COVID-19 and how some patients are actually showing clinical improvement as a result of the pandemic. Our aim is to heighten awareness of the interfaces between COVID-19 and SMI to facilitate informed treatment of people with SMI during this pandemic, with each hospital and outpatient setting knowingly modifying what it does to meet local needs.

Symptoms

The world's response to COVID-19 needs to be understood in the context of patients' symptoms as the symptoms can significantly alter what has been the general population's response.

Paranoia. Remote forms of communication can increase patients' paranoia as they are required to communicate through electronic tools—seeing their psychiatrist on a screen, for example. The fear experienced by staff is felt by patients whose paranoid thinking can be magnified. Staff: "Those in power are misleading us, particularly in light of the rapidly evolving (or perceived flip-flopping) responses

and parameters to dealing with the pandemic." Patients: "You're pumping the virus through the vents in my room because you want to kill us"; "The staff are all wearing personal protective equipment [PPE] and we patients will die so you can live."

Delusions. Besides beliefs about an evil government or an evil world, some patients have incorporated COVID-19 into their long-held beliefs such as the illuminati being in control of the world pandemic or the world's population deserving to be punished. Another example is a patient who believes she is a physician but is giving misinformed medical advice on COVID-19 to other patients on the unit.

Hallucinations. People with SMI may attribute information they receive to their "voices" or hear the viruses making noises. Most important is the need for the psychiatrist to be sensitive to the fact that auditory hallucinations can interfere with one's ability to communicate by telephone. The patient mixes up all the voices, including the psychiatrist's. The loss of visual cues may seriously compromise communication between doctor and patient that has previously been effective.

Cognitive deficits. Individuals with cognitive deficits may not understand what this is all about, leading to their inability to appreciate the seriousness of the situation. They may not remember what they've been taught about the virus and may require reminders multiple times a day to get them to adopt new habits such as washing their hands more often and practicing social distancing. Individuals with cognitive deficits can be incontinent, leading caretakers to have physical contact with the individual multiple times a day. And patients with cognitive deficits can be agitated, aggressive, and assaultive, again requiring caretakers to have physical contact with the individual multiple times a day. How do staff put someone in a hold or in restraints and maintain social distance? All staff need to be trained how to avoid being spit on by patients during these procedures.

Disorganization. Like those with cognitive deficits, disorganized patients may struggle with following procedures about hand hygiene and social distancing. They may also be confused about their stay in the hospital or why they can't have visitors. Real-time examples include a patient who assents to extend her stay in the hospital, then follows up with "I prefer to be discharged to go visit my family and check on them with this virus thing." Another patient said he had COVID-19, but despite having an unrealistic and incoherent story, this triggered a major staff response due to the potential backlash of ignoring such statements in light of the seriousness of the disease.

Anxiety. Patients with previous trauma symptoms or posttraumatic stress disorder (PTSD), especially complex PTSD, can be triggered by COVID-19 fears: "The hospital is no longer a place of safety"; "My therapist can't even meet with me in person"; "I was told, 'We don't have time for your cutting.' " Symptoms of COVID-19, especially shortness of breath, may compound anxiety and panic attacks that patients experience. This can lead to difficulties in breathing, confusing two origins for poor oxygenation. Anxiety can lead to ignoring early symptoms of the virus or to confabulating symptoms, with or without secondary gain.

Incidence of SMI

During this pandemic, it is reasonable to expect that new cases of SMI will arise and need to be addressed by the current psychiatric workforce. But there is reason to believe there will be additional cases that mimic or may in fact become SMI.

In 1919, Karl Menninger reported that as a result of the Spanish flu epidemic, infected people he saw at the Boston Psychopathic Hospital had psychotic symptoms that appeared to result from their infection (1). One-third of these patients were diagnosed as having schizophrenia (dementia praecox). Of the 50 of 175 cases that could be traced one to five years later, two-thirds had apparently recovered (2). Contemporary extensions of this work have found that "a recent onset of psychotic symptoms was significantly associated with coronavirus exposure as determined by bivariate analysis of quantitative antibody levels and

qualitatively determined seroprevalance" (3). This means that coronavirus exposure may be a comorbid risk factor in individuals diagnosed with SMI (3).

What this will mean in the context of COVID-19 is yet to be seen. Emergency departments (EDs), psychiatric units, and state hospitals might well see psychotic presentations in people with COVID-19 needing treatment, recognizing that these symptoms in all likelihood will not abate when the symptoms of the infection have dissipated. These individuals will need much longer-term follow-up for their psychotic symptoms.

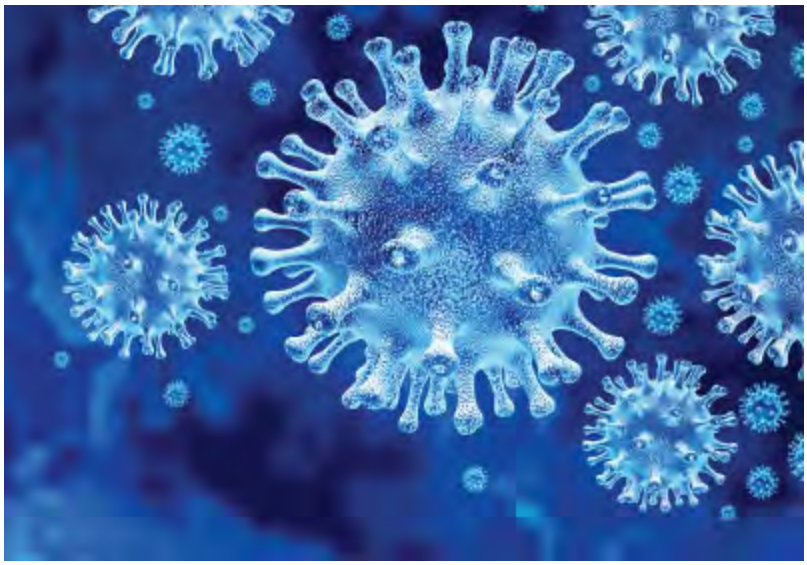
It comes as no surprise that anxiety is at high levels during the pandemic in the United States. One would expect that individuals will present with posttraumatic stress symptoms (PTSS). That is the finding coming from China, where women have experienced higher rates of re-experiencing trauma, negative alterations in cognition or mood, and hyperarousal (4). Many people will need acute treatment for these symptoms, and some will progress to PTSD and require long-term treatment. There is no way to know how many individuals who were coping adequately with PTSS prior to the pandemic will subsequently meet criteria for PTSD.

In health care workers exposed to COVID-19 in China, depression showed a rate of reported symptoms in a sample of 1,257, higher than any symptom other than distress, exceeding anxiety and insomnia (5). As with PTSS, some who develop depressive symptoms will achieve resolution of those symptoms through brief interventions, but others will progress to major depressive disorder and need longer-term treatment.

In addition, beyond fear of, exposure to, or actual infection by coronavirus producing psychiatric symptoms, the act of quarantine and isolation itself induces psychiatric symptoms. Quarantine will not only exacerbate symptoms in those with known SMI, but it also may bring to treatment people with SMI, who were previously undiagnosed and/or untreated due to exacerbation of symptoms.

Settings

Inpatient hospitals. Psychiatric hospitals have followed general hospitals in restricting who is going into the building and in setting up screening of those who enter. Psychiatric hospitals have to enact additional restrictions that limit the movement of patients within the building: In hospitals with multiple units, patients are being restricted to their own unit. Off-unit endeavors, such as group activities and meals, have moved onto the unit. Many of these units, especially those in newly constructed facilities, were never designed to have patients stay on them during the day as the model is off-unit programming. Increased restrictions and overcrowding lead to increased behavioral outbursts, leading to more staff involvement (for example, application of restraints), and hence increased staff exposure. Disrupting patterns of patients' meals increases the risk of choking and medically dangerous confusion of patients' diets. Poor hygiene in hospitals, where no windows are open and the air recycles through a ventilation system, is a heightened risk for, or is perceived by patients and staff to be a heightened risk for, viral transmission.



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Patients in psychiatric hospitals loan, exchange, barter, or steal possessions. These objects have been in the hands and against the faces of patients. Patients often share food despite rules forbidding it.

In states where "patients' rights" are paramount, sometimes at the risk of violating the general rights and safety of others, delayed response in implementing visitor restrictions and restrictions in incoming mail and food increases the risk of exposure throughout the facility. While perhaps not the highest priority, psychiatric hospitals need to have adequate PPE for their staff since the hospital is at high risk not only to have an infection sweep through it, but also to be a center that seeds a community.

Some states are considering or are implementing the placement of all of its coronavirus-positive patients at their public psychiatric hospitals into one of these hospitals. This is available only in states where there is more than one public psychiatric hospital and where geographic distances do not prohibit such an intervention. The challenges of completely isolating the coronavirus-positive patients and the staff who care for them from the hospital's other patients and staff are enormous.

With the outpatient community not able to accommodate discharges as it could before, patients' hospital stays are lengthened. Psychiatrists are making uncharted risk-benefit analyses: Is the patient and others at more or less risk if the patient stays in the hospital or if the patient is discharged with a less-than-optimal discharge plan? For example, should a patient originally planned to be discharged to a residential program be discharged to his parents' home instead because he would be at much lower risk for infection?

While far from extensive, there are some resources available to those working in state hospitals. The Substance Abuse and Mental Health Services Administration (SAMHSA) has a guideline, "Covid-19: Interim Considerations for the State Psychiatric Hospital," but it is cursory and needs to be quickly updated. A valuable resource from the Centers for Disease Control and Prevention is not directed at

state hospitals at all, but rather at correctional facilities: "Interim Guidance on Management of Coronavirus Disease 2019 (COVID-19) in Correctional and Detention Facilities." We make no statement here that state hospitals are like jails and prisons, but these are the best guidelines available that address how to manage a population locked in a facility in close quarters where all the previous day-to-day rules need to be changed. State hospital leaders can take from these guidelines whatever might work for them.

Community. With agencies providing community services operating on skeleton crews and/or with no face-to-face contact, how do individuals who have been dependent on these services for decades survive? What about patients without phones or who know nothing about their phone other than it is an instrument with which to make calls? One temporary change that should make communications easier among those providing services to people with SMI in residences, supported apartments, or in single dwellings is the relaxation of HIPAA standards for sharing information.

In some locations, such as in the greater New York City area, psychiatrists are switching patients they think can manage the change from long-acting injectables to pills so that they do not need to leave their residence to get a shot. Again, we are on a new frontier of risk-benefit analysis. If the result is a substantially greater number of psychotic decompensations, leading to more ED visits, then we have failed. If only a small percentage of those who switched need acute intervention and all the others have stayed home, then we've succeeded. At best we are making an educated guess for each individual.

Residential settings for individuals with SMI are doing preventive interventions, such as having residents spend very little time in common areas of the house, staggering mealtimes, and excluding all visitors. Residents who visit their family must remain with the family until the crisis is over. Some state departments of mental health have set up designated residences where individuals who test positive for the virus but are not in need of hospital care can live.

Shelters need to adjust business as usual: It has long been their practice to put people out during daytime hours; yet, they, too, may be facing problems with overcrowding and the inability to accommodate the same numbers of individuals. Unsheltered homeless people, at least one-third of whom have SMI, represent another problem because they often congregate at night in open-air locations. For example, on Massachusetts Avenue in Boston, homeless people still gather along the street, in close contact with each other and within half a mile (or less) of the Boston Medical Center.

Substance misuse is another problem in the community. The rate of sharing needles and joints may rise as supplies are harder to find. People with limited resources or those turned away because the pharmacy ran out of their medication are taking pills never prescribed for them. Given that care is being channeled to the COVID-19 crisis, to what degree are psychiatrists and others still paying attention to the opioid epidemic and the overdoses that were headlines just weeks ago or to the escalating death rates from benzodiazepines and methamphetamine? And people on opiates and benzodiazepines are at higher risk for respiratory compromise. We hardly need an increase in patients with severe respiratory depression from opiates competing with patients in severe respiratory distress from COVID-19 for the ED staff's attention. We need greater attention to substance misuse at this time, not less. To this end, the Drug Enforcement Administration (DEA), in its statement "Use of Telemedicine While Providing Medication Assisted Treatment," exempted DEA-registered practitioners from the in-person medical evaluation requirement as a prerequisite to prescribing or otherwise dispensing controlled substances. Furthermore, the SAMHSA recently announced increasing the first-year 30-patient limit for qualifying practitioners to a hundred if the need arises to meet demand. SAMHSA also released "OTP Guidance for Patients Quarantined at Home With the Coronavirus" and is permitting states to request blanket exceptions for all stable patients in an opioid treatment program (OTP) to receive 28 days of take-home doses and 14 days for patients who are less stable in their OTP.

Social isolation. For many persons with mental illness, being alone is a terrible burden, far beyond that experienced by many others. The costs of their loneliness are similar to those of many elderly Americans. Loneliness precipitates psychiatric symptoms in those without SMI, let alone those with these disorders. And the message can be quite confusing to the person with SMI: A clubhouse member living at home said, "For years they told me not to isolate myself and to be out with other people. Now they're telling me to stay home and isolate myself. I'm confused."

People in abusive households can be in danger from sources other than the coronavirus. They can be isolated with their abusers; tempers may flare, and violence could ensue. Their abuser may threaten them with eviction if they show symptoms. Among all the other reasons they have feared seeking help, they have a new fear of going outside and contracting COVID-19. Will we see more women with signs of severe physical trauma being pushed into EDs on stretchers? Will we have an increased rate of murder-suicides?

Medical Comorbidities

Physical health. Patients with SMI are particularly vulnerable to COVID-19 due to generally being in worse physical health than the general population. They typically delay seeking medical care for various reasons and have more medical comorbidities such as hypertension and diabetes (6). In addition to the widely recognized risk factors for COVID-19—diabetes, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD)—the American College of Cardiology also identified obesity and hypertension as risk factors for viral respiratory illnesses, including COVID-19 (7). CVD and its risk factors—psychotic illness being an independent risk factor for CVD (8)—are twice as high in patients with schizophrenia than in the general population (9). Likewise, obesity is twice as prevalent (10) and diabetes is at least three times as prevalent (11) in people with SMI compared with the nonpsychiatric population in all age groups.

Additionally, while the rate of smoking in the general population is about 18%, 53% of people with SMI smoke (12), and the rate of COPD is consequently similarly elevated at 22.6% compared with 5% in the general population (13). The medical needs and comorbidities of people with SMI cannot go untreated; otherwise, they will be yet another subpopulation streaming into EDs.

Medications

Antipsychotics. With heart disease and diabetes being major risk factors for severe COVID-19 infection, patients on antipsychotics ought to be considered high risk—a cumulative effect from having an SMI. Long known for their propensity to contribute to obesity, diabetes, and metabolic syndrome (14), antipsychotics also increase risk for hypertension, thrombo-embolic events, QTc prolongations, and change in endothelial function (15).

Additionally, antipsychotics have been linked to respiratory dysfunction and failure (particularly in patients with COPD) likely by causing improper respiratory muscle activity (16) or central respiratory depression (17). First- and second-generation antipsychotics are equal culprits in causing pneumonia, affecting not only elderly individuals, but young patients as well. Smokers, those with chronic respiratory disease, dysphagia, or cerebrovascular disease are particularly at risk. Treatment with multiple antipsychotics further increases the risk for pneumonia. How will those patients fair if they were infected with COVID-19?

Anxiolytics. Even before the COVID-19 pandemic, an increase in the prescription of benzodiazepines by primary care physicians was noted (18). With the rise in anxiety symptoms and diagnosable cases of anxiety disorders such as generalized anxiety disorder and PTSD, an increase in the prescription of anxiolytics followed. Knowing that benzodiazepines contribute to poor respiratory functioning (19), our patients are less able to fight a COVID-19 illness if infected. Alternatively, those unable to fill their long-term prescriptions on time at their pharmacy might either turn to illegitimate ways to obtain them or run the risk of abrupt withdrawal and experiencing seizures.

Side effects. Beyond the physiologic vulnerability to COVID-19 incurred by psychotropics, people with SMI are subject to other side effects that increase their risk of contracting and spreading the virus: sedation and drowsiness may lead patients to put their head on a table and fall asleep, creating face-to-surface contact in common areas. Involuntary movements cause more face touching and contact with others. Drooling from sedation or clozapine-induced sialorrhea (20) can quickly spread the virus over a wide area.

Medication interactions. Experimental drugs are currently used for COVID-19 treatment. Some have unknown side effects, while others can have serious interactions with psychiatric medications and other medications. For example, ritonavir is contraindicated with disulfiram (oral version has 42% alcohol) and decreases metabolism of midazolam and triazolam. Its level is decreased by CYP3A4 inducers such as carbamazepine, and it directly inhibits 3A4 and 2D6 through which several psychotropics are metabolized. The more famous combo hitting the headlines about COVID-19 treatment is made of two QTc prolonging medications: hydroxychloroquine and azithromycin, further increasing the burden on the heart of those on psychotropic medications.

Prejudice (Stigma)

We can anticipate an increased shunning of many people with SMI due to their looking like someone more likely to be infected and their appearance in general. It comes as no surprise that people quickly move away from someone who does not keep usual social distance from them even when there is no pandemic. Most problematic is perceiving people as unable to maintain social distance and handwashing practices just because they have a serious mental illness when, in fact, they are quite capable of doing so. Hospital staff, employers, and family members can be particularly susceptible to this.

Rationing of health care resources is already under discussion (21). Because individuals with schizophrenia have a shorter lifespan than that of the general population, will they be the last to receive treatment if the criteria for prioritizing

treatment "maximizes the number of patients that survive treatment with a reasonable life expectancy" (21)? The Office of Civil Rights of the Department of Health and Human Services has released guidelines saying that states, hospitals, and physicians cannot put people with disabilities at the back of the line for care. But will everyone adhere to that directive?

Benefits

Amid all these concerns during the COVID-19 pandemic, the symptoms and functioning of some psychiatric patients have actually improved when interventions are knowingly framed by their psychiatrist.

Suicidality. A 23-year-old tall, thin woman who has always felt very much alone in the world has been in the hospital since adolescence. She is afraid she'll die in some cataclysmic event. To avoid that, she states she will commit suicide if discharged; once alone on pass she had made a very serious suicide attempt. Her psychiatrist pointed out to her that now the whole world feels just like she does, and she is not alone. She has never functioned better than she has since she understood this.

Delusions. A septuagenarian Korean War veteran, with decades of delusions about federal government deceit and his suffering as a result of its lies, was informed that now a good percentage of the U.S. population also thinks the federal government is lying to them. He was asked if he could put aside his own grievance and take up the national grievance. With all his experience in writing thousands of documents about government deception, would he agree to be a consultant to the national effort? He did agree. He writes less. The national problem is addressed with meetings with his psychiatrist. He's engaged at a time when there's not much to do on the inpatient unit.

Paranoia. A 50-year-old never-married man on disability has, for two decades, gone to supermarkets at off hours to avoid as many people as possible. He goes down aisles when they are empty of people. He keeps his distance from store

personnel in the checkout line. He avoids other shoppers as they enter or leave the store. Now his behavior is normalized, and no one thinks twice about his behavior.

Negative symptoms of schizophrenia. A 62-year-old man who lives alone is a member of a very large Italian family, none of whom had ever moved far from their birthplace. The family gets together almost every week for a holiday or family event, and everyone has to come. Our patient, aware he has no ability to engage in social conversation, hates these gatherings. He describes them as "torture." He has never been more at ease in his life since there are no family get-togethers, and no one knows when there will be another one.

OCD. A 60-year-old woman who became disabled from her teaching job due to OCD symptoms has spent the last decade avoiding touching anything she didn't absolutely have to touch, washing her hands incessantly, and wearing some clothing only outside and other clothing only inside. She had garnered the pity of friends and relatives (which she hated). When she was out in public, people would get impatient with her or stare at her as she hesitated before going through doors or picking up items while figuring out how to minimize her exposure. Now, no one pays her any mind at all. Some people are actually mimicking her well-practiced moves.

Mental health support. As indicated by an APA poll released in March, anxiety about COVID-19 runs high among Americans, as does the sense that coronavirus is having a serious impact on their lives. Health care workers are proving to be especially vulnerable to showing elevated psychiatric symptoms. But while some services have become less available, others have been newly developed: The Texas Health and Human Services created a free, statewide, 24/7 mental health hotline to support Texans struggling with mental health repercussions of the COVID-19 pandemic. Will states that have not done so follow suit? Will individuals who were previously reluctant to seek psychiatric help find this pandemic a good reason to do so?

Conclusion

In this article, we have attempted to provide an overview of what is happening to people with SMI in this pandemic to better equip us all to more effectively deliver care and treatment to this vulnerable population. Like so many others in health care, we now find ourselves in rough waters with one broken oar in a craft that requires two paddles. In this health care crisis, psychiatry, like every other medical discipline, finds itself venturing forth in practice patterns with which we have no experience. We might do well to heed the words of Mahatma Gandhi: "You may never know what results come of your actions, but if you do nothing, there will be no results." ■

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EXHIBIT 31

Commentary: COVID-19

Perspectives on the COVID-19 Pandemic and Individuals With Serious Mental Illness

Ann K. Shinn, MD, MPH,[a]* and Mark Viron, MD[b]

Just over a month ago, the World Health Organization declared coronavirus disease 2019 (COVID-19)—the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)—a global pandemic.[1] The scale of disruption that the COVID-19 pandemic has had on society has been massive and unprecedented. As of April 16, 2020, the coronavirus has infected more than 2 million people and claimed the lives of 144,341 worldwide.[2] The statistics in the US alone (668,174 cases, 33,931 deaths)[2]—which now overshadow those in the first epicenters such as China, South Korea, Italy, and Spain—are sobering.

The major public health focus at the start of the pandemic was to "flatten the curve," or slow the rate of COVID-19 transmission, with a particular emphasis on protecting the elderly, the immunocompromised, and those with respiratory and other medical conditions that placed them at higher risk of more severe outcomes if infected. However, as we enter the second month of the COVID-19 shutdown and contend with the idea of a new "normal," the impact of the COVID-19 crisis on other vulnerable populations, including individuals with serious mental illness (SMI) such as schizophrenia and bipolar disorder, shifts into greater focus.

Impact of the Coronavirus on People With SMI

Potentially higher risk of coronavirus exposure and infection. Schizophrenia and bipolar disorder are associated with cognitive deficits, including executive dysfunction.[3] In addition, people with SMI comprise a disenfranchised group,[4] with lower educational attainment[5,6] and health literacy,[7–9] on average, compared to the general population. Such factors may make it harder for people with SMI to find accurate information about COVID-19 and to organize, appraise, and translate health information into behavior that reduces risk of exposure and infection. This is especially true given the speed and constantly evolving nature of new information and guidance about COVID-19, as well as the troubling amount of "noise" in the form of misleading or false information circulating in social media and even some mainstream news outlets.[10]

Negative health-related behaviors may also increase infection risk in SMI. Some studies suggest that SMI patients may have lower rates of adherence to treatment for medical conditions[11,12] (though data are mixed; see, eg, Kreyenbuhl et al[13]). Thus, it is possible that patients, especially those who are more acutely ill, may have a harder time complying with protective hygiene measures, stay-at-home orders, and other health guidance during this pandemic. Tobacco use is another adverse health-related behavior that is much more common in SMI (64% in schizophrenia and 44% in bipolar disorder vs 19% in individuals without psychiatric illness).[14] Contact with virus-contaminated fomites is one of the mechanisms of coronavirus infection, and the act of smoking, which involves the hands and possibly contaminated cigarettes and other smoking apparatus coming in frequent contact with the mouth, may elevate risk. In addition, the coronavirus uses the angiotensin converting enzyme II (ACE-2) receptor to gain entry into cells and cause active infection,[15,16] and it was recently found that smokers have higher expression of ACE-2 in bronchial epithelial cells compared to nonsmokers and former smokers.[17] The higher ACE-2 levels in the airways of smokers is thought to predispose smokers to coronavirus infection.

Finally, individuals with SMI face greater risk of contracting exposure and infection because of structural barriers that can hinder their ability to successfully quarantine at home. SMI is associated with higher rates of homelessness and unstable housing.[18] According to one estimate, 20% of schizophrenia and 17% of bipolar disorder patients are homeless.[19] These numbers suggest that a disproportionate number of patients with SMI may lack the basic necessity of a safe and secure location in which to practice social distancing. Furthermore, for patients residing in communal settings, such as shelters, psychiatric units, and group homes, there can be heightened risk of contagion, as occurred in South Korea, where 101 of 103 patients in a psychiatric unit contracted COVID-19 and 7 died.[20] Similarly, in New York, people with disabilities living in group homes were found to be 5.3 times more likely than the general population to develop COVID-19 and 4.9 times more likely to die from it.[21] Psychiatric units and other behavioral health settings are often designed to facilitate social interactions, with patients and staff interacting in close quarters. In contrast to medical floors, psychiatric units are less likely to be equipped with personal protective equipment (PPE), and staff may have less prior training and experience in infection control practices. These factors, compounded by the worldwide shortage of PPE and the ongoing difficulty of accessing testing, create daunting challenges for congregate care settings, where coronavirus infection in just one patient or staff member could spread rapidly and have life-threatening consequences.

Likelihood of poorer outcomes from COVID-19. The coronavirus causes severe illness—with complications such as pneumonia, acute respiratory distress syndrome, septic shock, and acute kidney injury—in approximately 16% of cases, according to data from early in the pandemic.[22] Severe cases are associated with the presence of coexisting conditions, such as diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease (COPD), immunodeficiency, and cancer.[22] Even without factoring COVID-19 into the calculation, SMI patients already have a mortality rate that is 3.7 times that of the general population, with the excess deaths largely attributable to cardiovascular and respiratory diseases.[23] Factors related to both illness (eg, physical inactivity due to negative symptoms) and treatment (ie, metabolic disturbances caused by atypical antipsychotic medications[24]) increase rates of cardiovascular disease and diabetes in patients with SMI. Tobacco use also causes lung disease and reduced lung capacity, increasing the risk of more serious illness. Even before COVID-19, the incidence of pneumonia was higher in schizophrenia,[25] and associated with antipsychotic medications[26,27] and tobacco use, among other factors. Furthermore, clozapine, which is the antipsychotic reserved for treatment-resistant schizophrenia patients, can suppress immune function and increase susceptibility to infections like pneumonia.

The reasons why underlying medical conditions cause more severe COVID-19 illness are not yet fully understood, but ACE-2, the receptor to which SARS-CoV-2 binds to cause infection, are highly expressed in the heart and lungs.[28] The coronavirus is thought to cause acute injury to alveolar and myocardial cells,[29] which may already be compromised in cardiovascular and respiratory diseases. The use of ACE-inhibitor antihypertensive medications, which up-regulate ACE-2, may also play a role in increasing the severity of infections.[29] Whatever the mechanism, the high rate of smoking and comorbid medical conditions in SMI, in combination with the medications routinely used to treat SMI, may create a perfect storm for COVID-19 complications.

Worse outcomes may also result from delays in getting treatment. SMI patients tend to present for medical attention much later in the course of disease. Difficulty recognizing and effectively reporting physical symptoms—whether due to reduced pain sensitivity,[30] anosognosia (impaired awareness of illness), cognitive and motivational impairments, delusional interpretations about the body, and/or denial[31,32]—may contribute. In addition, SMI patients tend to have less financial and other resources, live in poorer neighborhoods with less favorable patterns of use and access to care,[33] and receive lower quality medical care.[34] Unfortunately, in the case of such a highly transmissible virus like SARS-CoV-2, delays in diagnosis and treatment not only impact the health of the affected individual but also have ramifications for public health.

Impact of the Public Health Response on People With SMI

The massive changes in society in response to the COVID-19 crisis—eg, the mandated closure of schools and businesses, and the sight of normally busy urban areas relatively empty of cars and pedestrians—are unsettling and surreal. For people with psychotic disorders, the current circumstances may exacerbate feelings of perplexity, anxiety, and paranoia and may also become integrated into the content of delusions. The lack of clear and consistent messages from the federal and some state governments add to the effects of social media misinformation campaigns and further contribute to confusion and instability in day-to-day life. So much is unknown not only about the new SARS-CoV-2 and the ultimate toll it will exact on human life but also about the scope and duration of mitigation efforts, which continue to be moving targets. The pervasive uncertainty about what to expect and how long the shutdown will last is a major source of distress for many.

While social distancing is necessary to protect public health, it can also have unintended effects. A subset of SMI patients may be less impacted by public health restrictions, having lived "socially distanced" lives for years, with minimal contacts outside of their immediate environment and necessities, whether as a result of symptoms, societal marginalization, or personal choice. But for many others with SMI, isolation measures further reduce and collapse social networks, which are often already tenuous. Social distancing limits access to treatment and support centers, including mental health providers, day programs, clubhouses, and peer-run respites. People in congregate care settings as well as their families and loved ones are now enduring increasingly prohibitive visitor policies. Simple but meaningful daytime routines such as visiting a favorite coffee shop, restaurant, or the library are now impossible.

Finally, the economic toll of the shutdown may be more pronounced for people with SMI. From mid-March to mid-April of this year, over 20 million Americans claimed unemployment.[35] People with SMI are more likely to have jobs that do not provide health benefits or paid sick leave and that are more vulnerable to layoffs and furloughs during the COVID-19 shutdown. While there are now talks about reopening the economy in certain states, the emotional, social, health, and financial impacts of this pandemic could act as traumas with enduring effects that will need continued attention even after the shutdown ends.

Impact of Changes in Health Care Delivery

In response to the pandemic, community-based behavioral health providers have been forced to shift from in-person, face-to-face services to "virtual" visits done by telephone or videoconference. This seismic shift in the landscape of behavioral health care has significant implications for people with SMI. Telehealth approaches have enabled ongoing access to vital services while helping to limit the spread of the virus. Telehealth has generally been found to be feasible and effective in treating mental illness and acceptable to people with SMI.[36,37] Mobile phone ownership (including smartphones) is increasingly common in all populations, including people with SMI, and evidence suggests that concerns regarding patients' ability and comfort using such technology may be unfounded.[38] Still, there will be individuals who will have difficulty or discomfort conveying information by telephone or videoconference. And while videoconferencing can improve the relational connection, there is a sense of "with-ness" that is lost in virtual interactions, and this phenomenon may disproportionately affect people who historically struggle to engage with their treaters. Issues of access and equity will come into play, as some people will not have the resources to obtain phone or Internet service, may lack enough minutes or data on their plans, or may not have the tech-literacy to participate in a video call without assistance. Other access issues to consider include the need to have workflows and technology that allow for the proper use of interpreters, including those for deaf and hard of hearing populations.

Like many others, people with SMI may forgo needed care out of fear of contracting the coronavirus in settings such as emergency departments, hospitals, outpatient laboratories, and pharmacies. Providers may need to reconsider the necessity and frequency of routine laboratory work in order to limit potential community exposure to the virus. Risk-benefit discussions will need to be undertaken with patients in order to assess the value of current monitoring protocols in the setting of a pandemic. The US Food and Drug Administration has released guidance highlighting flexibility in clozapine monitoring requirements during the COVID-19 public health emergency.[39] To ensure medication adherence is not interrupted, patients may need

assistance programs, home deliveries from pharmacies). The formulation of long-acting injectable medications may also become challenging due to staffing issues and inadequate PPE, necessitating creative problem-solving and possible return to oral medication for a period of time.

Conclusions and Recommendations

The COVID-19 pandemic presents challenges for us all. However, people with SMI may face even greater challenges due to the multiplicity of factors that put these individuals at risk for coronavirus infection and complications, as well as the massive impact of public health measures and associated changes in mental health care delivery. These factors are likely additive and make an already marginalized segment of society even more vulnerable. There is no doubt that this pandemic is causing devastation worldwide, but the pandemic arguably does more to expose problems that already exist. According to historian and writer Frank M. Snowden, epidemics like the coronavirus are "a mirror for humanity."[40] He writes, "Epidemic diseases are not random events that afflict societies capriciously and without warning. On the contrary, every society produces its own specific vulnerabilities."[40] In the case of people with SMI, what is reflected is the profile of a vulnerable population in a health care system that is highly fragmented.

What can we do about this? First, we need to creatively and actively engage and strengthen partnerships with patients, whether through virtual encounters or in-person with the protection of PPE (eg, for congregate care settings) during this period of social distancing. Patients may need increased support to cope with the stress and uncertainty of the pandemic and to manage any exacerbation of symptoms. Importantly, we need to ensure that patients receive clear and accurate information and education about COVID-19 and how to protect themselves and those around them from disease transmission. Health information needs to be presented and represented in clear and accessible ways, tailored to individual strengths and limitations.

Until vaccines become available, close monitoring of physical health and increased access to testing will be critical, while recognizing that treaters may need to advocate for their patients in order to secure appropriate COVID-19 testing. Those living in congregate care settings will need to be supported by staff who have been trained to monitor for signs and symptoms of COVID-19, including the identification of symptoms requiring emergent attention. People with unstable housing will need suitable accommodations to ensure the safety and health of themselves and others. People who are unable or unwilling to follow public health guidance and restrictions such as quarantine or isolation will pose special challenges to the system of care, necessitating supportive and individualized approaches that will hopefully avoid more restrictive or drastic measures that could be undertaken in order to protect the health of the individual and public.

Given the likely increased risks of negative outcomes from COVID-19, as well as the difficulty some individuals have in recognizing and communicating physical symptoms or health needs, people with SMI who are at risk for or have been diagnosed with COVID-19 may need closer medical monitoring if quarantining or isolating outside of a hospital setting. In all these efforts, close collaboration between psychiatry, primary care, and other medical services is needed to reduce poor clinical outcomes in this vulnerable population.

Second, the health care system, and society more generally, needs to not only deal with issues related to COVID-19 but also address the deeper challenges and disparities that people with SMI face. We need to help patients achieve better health outcomes through smoking cessation, improved diet and exercise, more effective medications with better side effect profiles, better access to quality health care, more stable housing, safer neighborhoods, and improved educational and vocational opportunities to increase social capital. We recognize that these goals are ambitious and unlikely to occur overnight. However, if we can use the current crisis to initiate sweeping change, as many clinics and hospitals have been able to do with the rapid transition to telehealth, we may find ourselves facing a less troubling situation in the "mirror" if and when another pandemic occurs.

Last but not least, we need to better understand some of the unique issues facing this population and stay vigilant regarding consequences of our actions or inactions in the months ahead. This will require going beyond making conjectures about potential

risks, as we do in this commentary, to collecting data to measure the actual health, emotional, social, and economic impacts of the COVID-19 pandemic on people with SMI.

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EXHIBIT 32

AMEND
CHANGING CORRECTIONAL CULTURE

Berkeley Public Health

Urgent Memo

COVID-19 Outbreak: San Quentin Prison

June 15, 2020

San Quentin California State Prison is experiencing a rapidly evolving COVID-19 (SARS-CoV-2) outbreak with profoundly inadequate resources to keep it from developing into a full-blown local epidemic and health care crisis in the prison and surrounding communities. The urgent resources San Quentin requires range from human capital to environmental risk reduction and rapid testing. Failure to meet these urgent needs will have dire implications for the health of people incarcerated at San Quentin, custody, staff, and the healthcare capacity of Bay Area hospitals. This document provides suggested guidance on immediate actions needed to address the outbreak with emphasis on both the short- and longer-term health of people currently incarcerated at San Quentin.

Background

San Quentin arrives at this tenuous moment with several significant assets including a strong Chief Medical Executive (Dr. Alison Pachynski) and a Chief Physician and Surgeon (Dr. Shanon Garrigan) who have spent the past 3.5 months doing everything in their power to prepare for an unavoidable COVID-19 outbreak. However, these two physicians, even with the enormous assistance they have received from many other healthcare staff, including a strong public health nurse, and a notably excellent partnership with custody leadership (Acting Warden Ronald Broomfield and the recently arrived Health Care Chief Executive Clarence Cryer), is simply not enough to meet the needs at San Quentin. As a result, there are multiple vulnerabilities that we witnessed at San Quentin during our visit on June 13, 2020 which must be urgently addressed to protect the health and safety of the thousands of people incarcerated there as well as staff and surrounding community members.

Although this memo outlines the urgent needs of San Quentin Prison, it is our belief that most – if not all – of these recommendations are important for all California Prisons that are certain to experience an outbreak if they have not already.

Urgent needs and immediate actions required:

1. **Develop a COVID-19 Outbreak Emergency Response Team:** At present, the over-reliance on existing local medical and custody staff to develop an outbreak response plan means that they are tasked with making multiple acute decisions on a daily basis without adequate resources, options, or support to operationalize a centralized plan or long term strategy. This responsibility – overwhelming on its own – is then magnified with the additional necessity of providing

implementation oversight of the ad-hoc outbreak plan. Instead, local leadership should have a team of staff who can implement and recommend adjustments to the overarching central COVID-19 control strategy as needed on the local level. There simply do not appear to be sufficient on-the-ground staff who are not working from home. This daily management of the acute phase of the outbreak has the secondary effect of making the lead physicians less available to coordinate the care and treatment of patients incarcerated at San Quentin who become acutely ill in the facility and also increases the vulnerability of San Quentin to errors with potentially dire consequences. Minimum positions required for such a team are included below. Dr. Pachynski and Dr. Garrigan appear to be personally responsible for all of the tasks described below with insufficient tools to support their success. While there may be some central guidance and support offered, additional human capital is urgently needed to achieve the CCHCS's pandemic response goals.

Minimum Recommended Leadership Team Positions:

- **Environment of Care Leader.** This position would be responsible for evaluating and addressing immediate needs regarding the physical plant of the prison for ventilation, sanitation, path of patient flow (e.g., developing policies and procedures for how people incarcerated at San Quentin who become infected are transferred through and out of the institution for care) and planning for how to reconfigure and reimagine needed space for quarantine, general population, or medical isolation units depending on how the number of affected people increases or decreases over time. This position would also work with plant operations to ensure that all air vents are cleaned and well functioning and would organize the creation of (a) field hospital(s) or quarantine tents as needed.

- **Healthcare – Custody Coordination Leader.** This position would focus on coordinating with Custody (and working closely with the Staff Healthcare Liaison Leader, described below) to review current placement on a daily basis, and to determine the appropriate way to cohort people currently incarcerated at San Quentin, staff, and custody including developing quarantine areas (in partnership with the Environment of Care Leader) to minimize risk of infection. This position would also be responsible for ensuring that all transfers *into* San Quentin are halted and that appropriate and timely testing is done to facilitate transfer out of Medical Isolation and Quarantine within the facility, to the community, and – in certain circumstances - to other facilities if medically necessary.

- **COVID-19 Testing Leader.** This position would be responsible for coordinating with the testing center (at this moment, QUEST Diagnostics) including reaching out through public and private sources and coordinating with the state and local departments of public health to improve testing turnaround time, running the list with medical staff (and the Epidemiologist, described below) on a daily basis to determine who has – and who needs – testing, and coordinating contact tracing in response to testing results and reporting of symptoms throughout the facility.

- **Staff Healthcare Liaison Leader.** This position would work with custody leadership (and Union representatives, as appropriate) to cohort staff/custody, develop plans that eradicate staff/custody working within more than one unit in rapid succession, train and enforce PPE rules, support contact tracing and administrative leave needs among exposed and infected staff/custody, and investigate alternatives to potential staff/custody transmission opportunities such as shared vanpools. This position would also track daily staff movements in order to assist with contact tracing when needed.

- **Epidemiologist Analyst Leader.** This position would be responsible for maintenance of a line listing of all active and resolved cases (people incarcerated at San Quentin and staff) and for all data analysis and reporting. This position would also be responsible for a "patient tracking process" of the facility including daily review of the COVID-19 Monitoring Registry to provide close scrutiny of who has tested positive or is in quarantine – where they are currently located (and were recently located), and the same for those who have tested negative. In addition, this position would assist the Environment of Care leader and the Healthcare – Custody Coordination Leader to manage patient movement to quickly clear people when they have tested negative and return them to the General Population and/or to the community. This position would also manage testing data (e.g., in the Reception Area, some have been tested 3-4 times and test results are coming in at different times).

2. **Address Unsafe Overcrowding.** There are currently 3547 people in total incarcerated at San Quentin, approximately ~1400 of whom have at least one COVID-19 risk factor (as do many, unknown, staff members). This means these individuals are at heightened risk of requiring ICU treatment and/or mortality if infected. We detail the units of most immediate concern below. Given the unique architecture and age of San Quentin (built in the mid 1800s and early 1900s), there is exceedingly poor ventilation, extraordinarily close living quarters, and inadequate sanitation. **We therefore recommend that the prison population at San Quentin be reduced to 50% of current capacity (even further reduction would be more beneficial) via decarceration**; this will allow every cell in North and West blocks to be single-room occupancy and would allow leadership at San Quentin to prioritize which units to depopulate further including the high-risk reception center and gymnasium environments. It is important to note that we spoke to a number of incarcerated people who were over the age of 60 and had a matter of weeks left on their sentences. It is inconceivable that they are still in this dangerous environment.

Housing units of most concern at San Quentin at present time:

- **North Block and West Block** have cells with open-grills, and are each 5-tier buildings with a capacity of 800 persons. Ventilation is poor – windows have been welded shut and the fan system does not appear to have been turned on for years; heat on the far side of the building can be stifling. Over 50% of those incarcerated in these units have at least 1 COVID-19 risk factor, and an alarming ~300 have 4 or more COVID-19 risk factors. An outbreak in North and West blocks could easily flood – and overwhelm – San Quentin as well as Bay

Area hospitals. (For example, see San Francisco hospital capacity: https://data.sfgov.org/stories/s/Hospital-Capacity/qtdt-yqr2/)

- **Reception center** currently has ~500 persons. In the reception Center's "Badger Unit" where people from CIM were transferred, the fear and outrage among the people incarcerated are palpable – people are yelling throughout the housing unit due to discontent about the COVID-19 situation including intake of transfers from CIM and loss of privileges/disruption to daily routine (thereby increasing the risk of COVID-19 spread throughout the tiers via respiratory droplets). It is hard to imagine that as a result of these conditions, that violent incidents will not occur—further threatening the safety and health of the people incarcerated in these units and staff alike.

- **The Gymnasium**, which has been converted to a dorm. There is little to no ventilation in this unit creating high-risk for a catastrophic super spreader event.[1] At a minimum, the gymnasium beds should be spread out more to ensure additional distance between beds, and the second set of doors in the gymnasium dorm must be opened to ensure air turnover. **This unit should be prioritized for closure as a dorm, once sufficient population reduction has been achieved through release.**

- **HVAC – in all units above and in other areas,** there is an immediate need to clean and turn on all fan and HVAC systems immediately (e.g., North Block, Gymnasium, Dorms) in order to maximize air exchange and ventilation as soon as possible. Of note, the exhaust pumps and filters appear dirty on visual inspection, and require clearing and cleaning. Since maximizing air exchange through better ventilation decreases COVID-19 transmission, doors and windows should be opened as much as possible (some have been welded shut and must be remediated). Note that the important aspect is *air exchange*, not the movement of air within the room. Fans that blow air around may help cool people, but they don't decrease rebreathing aerosols unless they filter the air or increase air exchange (diluting the aerosol).

3. **Immediately Improve Testing.** It is inconceivable that in the Bay Area the medical leadership at San Quentin is having to manage an outbreak in their massive antediluvian facilities with PCR tests on a 5-6 day turn-around time. We would argue that there is no higher testing priority for around 100 miles and resources need to be shifted immediately to respond or there will be a massive, uncontrollable outbreak (if it is not too late already). In addition (and this certainly goes without saying), **transfers into San Quentin must be halted immediately**. **Further, priority must be placed on reducing the prison population at San Quentin via decarceration as it will be extremely difficult to ensure the health and safety of all people in this extraordinarily old and**

[1] It is important to recognize that all of our recommendations regarding ventilation in different housing units at San Quentin were based on the observations of a team of public health professionals accompanying San Quentin medical staff. Although incarcerated persons and custody staff shared their understanding of the ventilation systems in the units and their operability, we neither had the opportunity to speak with any of the facilities staff nor were any members of our team experts in HVAC. We would strongly recommend seeking the advice of such experts and monitoring CO2 levels in different parts of the prison as one easy measure of the extent of rebreathing in a housing unit.

complex facility. The following recommendations both support these imperatives and, in some cases, are dependent on their implementation:

- **Liaise with testing laboratory to streamline testing,** including exploring observed self-collection of samples and alternate anatomic sites of testing (e.g. saliva, nares swabs).

- **Improve testing turnaround time at QUEST or go through other laboratories that will be able to improve turnaround time (5-6 days or more is completely unacceptable).** As an example, CMC was able to rapidly respond to their outbreak with a turnaround testing time of 24 hours at some points in the outbreak. Large-scale testing with rapid receipt of results is essential to allow the medical team to minimize community spread. If tests are sent to laboratories other than QUEST, support must be provided to San Quentin to add these results to the EMR as the current process of scanning and manual entry is overly laborious and resulting delays may lead to medical decisions based on outdated data.

- **The California Department of Public Health** should be compelled to prioritize specimens from San Quentin given the potential for super-spreading in that environment.

- **Testing of symptomatic patients must be done with individual testing. Testing of asymptomatic patients to identify people who are shedding virus can be done with pools of samples. Without additional information, pools of 10 should be used.** This approach can be used for frequent retesting of people at especially high risk of spreading the virus (staff/custody and people incarcerated in larger units — i.e. almost all of San Quentin).

- **San Quentin requires on-site testing –** including cartridges and well-trained staff to conduct these (currently they have inadequate staffing to conduct mass swabbing). Sample transport just adds time. San Quentin will need high volume testing for many months, perhaps years. They should have testing capacity on-site and available round-the-clock.

- **Of note, because testing time is so slow, little to no contact tracing can happen. Furthermore, people incarcerated at San Quentin cannot be appropriately transferred within the prison based on test results if results are returned 6 days later and new exposure may have occurred in the interim.** As a result, *entire units are put on lockdown status for the span of a quarantine*. This is not a viable solution. In the long term, as this pandemic will last at least another year and likely longer, this will have profound physical and mental health consequences for the incarcerated population and staff alike.

4. **Develop Additional Medical Isolation and Quarantine Housing.**

Background: It is our understanding that on May 30, transfers from CIM arrived at San Quentin on five buses. Several among those who were transported on Bus 5 tested positive at arrival. While all transfers on Bus 1 and 3 initially tested negative, several later developed COVID-19 symptoms. At the time of our visit, there were no reports of symptoms or positive tests among those who traveled on Buses 2 and 4. At the advice of the local health

department, all individuals from the five CIM buses who tested positive or reported symptoms were placed in the Adjustment Center. Those who either tested negative or did not report symptoms were placed individually and in every other cell on the Reception Area's Badger and Donner Units 4th and 5th tiers (among people who were incarcerated at San Quentin prior to the transfer).

June 13 Visit: As of our visit, those requiring *Quarantine* (i.e., people with a credible exposure to COVID-19 who are asymptomatic) are in the Reception Area's Carson Unit. Those requiring *Medical Isolation* (who have tested positive for COVID-19 **or** who have symptoms suggestive of COVID-19 and are still awaiting testing) are in the Adjustment Center as this is the only unit at San Quentin that has single cells with solid doors. Per our notes, there are ~106 cells in the Adjustment Center, with ~80 occupied at the time of our visit.

Urgent Concerns:

1. A massive outbreak at San Quentin will significantly and quickly overwhelm the availability of these 106 Adjustment Center cells, and there will quickly be nowhere for infectious cases to be moved. Further, we cannot emphasize enough the incredible fear that residents we spoke with expressed about being moved to cells typically used for administrative segregation/punishment or "death row" – potentially resulting in short- and long-term mental health consequences. Especially given that early identification of suspected COVID-19 cases depends on reporting of symptoms, **quarantine strategies relying on the Adjustment Center or cells usually used for punishment may thrwart efforts for outbreak containment as people may be reluctant to report their symptoms**. In addition, people with COVID-19 are known to experience rapid physical decompensation; it may therefore be particularly detrimental for a patient with COVID-19 to be behind a solid door in the most secure areas of the prison out of the sight of medical or nursing staff in the case of an emergency. This may be particularly risky if there are structural barriers to communicating distress to staff (e.g., if accomodations are not readily accessible for people with disabilities or who speak other languages, and/or there are multiple security stages to pass through).

Given San Quentin's antiquated facilities, poor ventilation, and overcrowding, **it is hard to identify any options at San Quentin where it is advisable to house high-risk people with multiple COVID-19 risk factors for serious morbidity or mortality**. Again, for these reasons it will be exceedingly hard for medical staff to keep people safe from contracting COVID-19 at San Quentin and, once infected, it will be very hard to ensure that they do not pass the infection on to others with high health risks or experience rapid health declines themselves. **San Quentin is an extremely dangerous place for an outbreak, everything should be done to decrease the number of people exposed to this environment as quickly as possible.**

Our recommendations for Quarantine and Medical Isolation are as follows:

- Immediately create a field hospital by **converting nearby chapels (there are 3) or even the chow hall.** This field hospital can be designated for all people with confirmed COVID-19 ("Medical Isolation Unit") as there are not substantial risks to isolating infected patients together and these patients would then have access to supervising nurses who could regularly check their respiratory status and comfort levels. Such a unit could have different tiers of medical supervision as some people in medical isolation will be asymptomatic and will not require as close medical supervision. The chapels are large rooms with road access for ambulances and other transport. We recognize the plans for assigning units will become increasingly complex as people of multiple security levels require Quarantine or Medial Isolation. **This again reinforces the need for release** and a dedicated team leader (the **Healthcare – Custody Coordination Leader)** who oversees the work of partnering with custody to identify medically appropriate cohorting solutions.

- **For those currently in the Adjustment Center:** As individuals test negative (via recovery or because they never developed infection) they ideally should be moved out of the Adjustment Center as quickly as possible. However, with evidence of community spread at San Quentin, extreme caution must be exercised when moving persons out of the Adjustment Center who test negative for COVID-19 and who are at high risk for poor health outcomes if infected. For these individuals, we strongly recommend that central administration work with medical leaders at San Quentin to identify options for safer placement of individuals leaving the Adjustment Center (perhaps in temporary tents) or in other CDCR facilities (transfers would have to happen with exceptional caution given prior failure with transport including 2 weeks of quarantine on either side of transfer coupled with testing at the outset and end of 14-day quarantine in each site). Alternative housing options outside of San Quentin should also be explored, including nearby hotels or school dorms that can be converted in an effort to save lives. People at the Adjustment Center who test positive should be immediately moved to the new Medical Isolation Unit (e.g., in the converted chapels).

- **Physical and mental health during quarantine and medical isolation must be prioritized with adequate consideration for how need may vary across people incarcerated at San Quentin.** While awaiting testing results, people should receive resources to support their well-being as much as possible during isolation/14-day quarantine period (quarantine should not exceed 14 days after a single exposure). Such resources, at a minimum, should include free access to personal tablets with movies, increased access to free canteen items, personal effects and free phone calls, perhaps on state-owned cell phones, and daily opportunities for yard time. While some of these comforts may seem beyond the normal routine of prisons in California, they are simple, low-cost measures that are essential if there is any hope of minimizing the risk of adverse short- and long-term physical and mental health outcomes of isolation among those who are currently in the Adjustment Center for

quarantine or isolation. Alternatives for isolation or quarantine that do not involve the Adjustment Center must be immediately sought (e.g., quarantine tents or other areas of the prison where significant depopulation can allow for fewer occupied cells). **Ultimately, there are simply too few options for safe quarantine at San Quentin without prioritizing population reduction through release.**

5. **Improve General Prevention efforts throughout the facility.** In particular, we witnessed alarmingly suboptimal mask use by staff, and three "medical pass nurses" sitting in a work room without masks. Moreover, custody work stations are not set up to physically distance, no additional workstations appear to have been built yet. As a result, even with the best of efforts, officers wind up clustered near each other around a central podium. An infection control nurse and environmental assessment would go a long way towards identifying opportunities to partially alleviate these problems.

6. **Staff Cohorting is a necessity.** At present work shift plans are inadequate from a public health perspective. For example, we learned about staff who were working in the Medical Isolation Unit (Adjustment Center) during the shift and were scheduled to work the next shift in the dorms. This is an enormous risk for the spread of COVID-19 between units.

7. **Convene COVID-19 Inmates Council.** To ensure urgent health messaging is comprehensively communicated through trusted paths, we recommend that a COVID-19 Inmates Council be established (if one does not yet exist) in collaboration with any existing leadership groups/councils among people incarcerated at San Quentin. This council should be asked to provide critical feedback regarding all the above recommendations, how they may best be implemented and messaged to the population, and if there are considerations that have not been addressed that will maximize the urgent and long term health needs associated with this outbreak.

8. **Convene COVID-19 Inmate Family Council.** To ensure urgent health messaging is communicated to the families of people incarcerated at San Quentin, we recommend that a COVID-19 Inmate Family Council be established. This council may also provide critical feedback regarding all the above recommendations, how they may best be implemented, and if there are considerations that have not been addressed that will maximize the urgent and long term health needs associated with this outbreak.

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Amend at UCSF is a health-focused correctional culture change program led by experts in medicine, infectious diseases, public health, and correctional health and policy that is providing correctional leaders, policymakers, and advocates the evidence-based tools they need to protect the health and dignity of those who live and work in jails and prisons during the COVID-19 pandemic.

The University of California, Berkeley School of Public Health is working on the leading edge of research, educating the public, and mobilizing to serve California's most vulnerable populations during the COVID-19 pandemic.

For more information:

https://amend.us/covid

EXHIBIT 33

AMEND
CHANGING CORRECTIONAL CULTURE

The Ethical Use of Medical Isolation – *Not Solitary Confinement* – to Reduce COVID-19 Transmission in Correctional Settings

***April 9*, 2020**

David Cloud, JD, MPH, Dallas Augustine, MA, Cyrus Ahalt, MPP, & Brie Williams, MD, MS

What is covered in this brief

This brief clarifies the differences between "medical isolation," "quarantine," and "solitary confinement," and describes the services and benefits that corrections officials should provide to people who are separated for medical isolation or quarantine so that they are not subjected to punitive and traumatizing conditions of solitary confinement. It is intended to provide guidance to departments of correction, prison and jail residents, advocates, and other key stakeholders to help ensure that using medical isolation or quarantine to mitigate the spread of COVID-19 in correctional facilities follow the highest standards of medical ethics.

The distinction between "solitary confinement", "medical isolation", and "quarantine"

- **Solitary Confinement** is the practice of isolating incarcerated people from the rest of the prison population while simultaneously imposing punitive measures such as major restrictions on visitors, phone calls, recreation and outdoor time, and access to personal property.
- **Quarantine** is the practice of separating and restricting the movement of people who may have been exposed to a contagious disease until results of a laboratory test confirm whether or not they have contracted the disease. These individuals may have been exposed to COVID-19, for example, by spending prolonged time in close proximity to someone who has tested positive, or they may have early symptoms of a potential COVID-19 infection.
- **Medical Isolation** is the practice of isolating incarcerated people from the rest of the prison population when they show signs or test positive for COVID-19 in order to stem the risk of COVID-19 transmission throughout the prison.

The ease with which COVID-19 can spread in prisons and jails

The millions of people incarcerated in the U.S. are particularly vulnerable to infection, illness, and death from COVID-19, due to high rates of underlying medical conditions coupled with confinement in crowded and often unsanitary conditions with limited access to personal hygiene products. As the World Health Organization (WHO), Centers for Disease Control (CDC) and many others have emphasized, social distancing, regular handwashing, and frequently sanitizing living spaces are essential to preventing the spread of COVID-19 and "flattening the curve" (or delaying the

transmission of disease in order to distribute the need for life saving healthcare resources over time rather than all at once). **Unfortunately, it is virtually impossible to follow these directives in many correctional facilities**, where hundreds and even thousands of people are confined in overcrowded, often unsanitary conditions—and where people generally lack sufficient access to soap, sanitizer, hot water, and other materials necessary to minimize the risk of COVID-19 infection.

Many public health experts, policymakers, advocates, and community leaders have called for the swift release of as many people as possible from correctional facilities in order to mitigate the accelerated spread of the virus among incarcerated people, correctional workforces, and the larger community. Increasingly, state and local leaders are heeding this call. These actions will surely prevent infections, alleviate suffering, save lives, and help "flatten the curve" inside and outside prisons and jails. However, the number of people released to date has been relatively small. Millions of people will remain in custody as COVID-19 continues to spread. **Some of these individuals will require temporary quarantine or medical isolation to stem the transmission of COVID-19.**

The complexity of using isolation as a tactic to minimize COVID-19 transmission in jails and prisons

1. **Placing people in solitary confinement (punitive isolation) will worsen the COVID-19 crisis.** Many corrections officials lack guidance on how to humanely and effectively separate sick or contagious individuals from the general population. At times, the most feasible and only available housing units in jails and prisons for medical isolation or quarantine of sick patients are those used for punitive solitary confinement in "normal" times (single cells, solid cell doors rather than barred, removed from the main center of the prison). Use of these units for medical purposes, while often necessary, can run the risk of corrections officials falling back on regular policies and procedures governing living conditions in these units that harm the health of those exposed. (see figure for policy differences)
2. **Fear of being placed in solitary will deter people from reporting symptoms to correctional staff.** Experts and advocates are deeply concerned that incarcerated people, many of whom will go to great pains to avoid solitary confinement due to well-established mental and physical health harms associated with the experience, will not come forward when they have symptoms of COVID-19 because they do not want to be placed in such conditions. This avoidance of reporting symptoms or illness will not only accelerate the spread of infection within facilities but also increase the likelihood of prisoner deaths due to lack of treatment.
3. **Preemptive lockdowns may result in failure to detect symptomatic people and cause undue stress to residents.** Some correctional facilities are preemptively placing entire units or facilities on "lockdown" for indefinite amounts of time, meaning that people are confined to a small cell, alone or with another person nearly all the time. Meals, medications, commissary, and other goods are delivered to the cell door. Recreation, programming, educational and religious services are shut down. As a result, interactions with correctional staff and healthcare staff often become less frequent and people with symptoms may go undetected.

During the COVID-19 crisis, medical isolation and quarantine should be used only as medically necessary, and these procedures should result in living conditions clearly distinct from those found in solitary confinement (see figure)

COVID-19 presents daunting public health challenges both inside and outside correctional facilities. **Separating people who become infected is a necessary public health challenge, particularly in prisons and jails. But turning to the punitive practice of solitary confinement in response to the COVID-19 crisis will only make things worse**. Research shows that keeping people socially isolated in a closed cell without a meaningful opportunity to communicate with family, friends, and loved ones or to participate in exercise, educational, and rehabilitative programming (solitary confinement) causes immense, and often irreparable, psychological harm. Emerging evidence suggests that the COVID-19 pandemic will last for at least several more months. Moreover, some people in prison will hide symptoms to avoid being housed in such damaging conditions, even if only temporarily. To minimize the risk of worse health among incarcerated people we recommend the following:

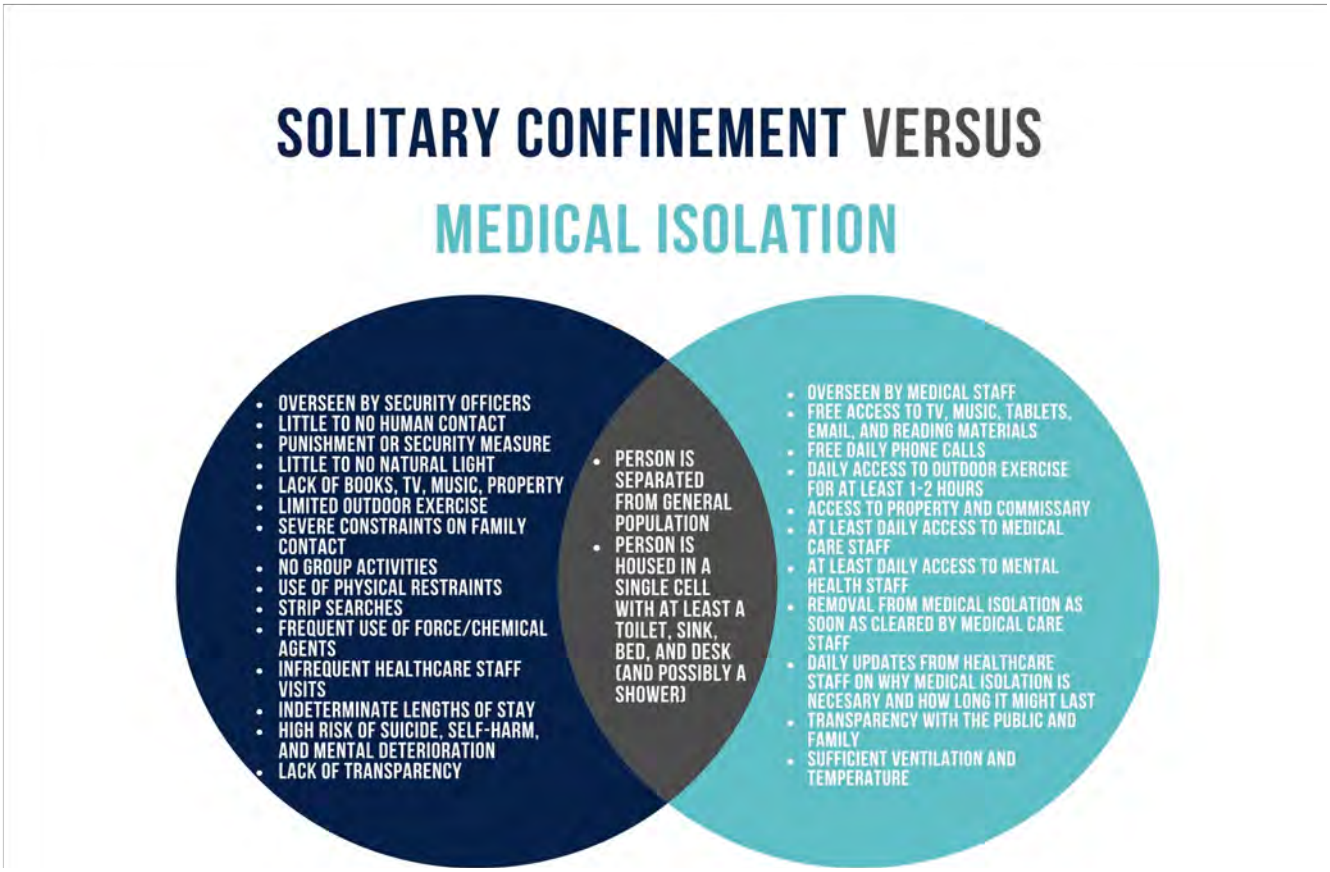
- **The purposes and practices of medical isolation and quarantine should be clearly described** to incarcerated people and their advocates, as well as to the corrections staff that oversees them.

- Corrections officials should only require people on an entire housing unit to stay in their cells ("Lockdown") **if medical professionals determine a symptomatic person resides or works on that unit or contact tracing flags a confirmed or suspected case**.

    - In this event, **time-limitations must be clearly communicated to residents and staff.** Based on current evidence, 5 days is the average time from exposure to symptom onset of COVID-19, and 97.5% of people show symptoms within 11 days. Depending on how evidence emerges in the weeks to come, unit-specific lockdowns could reasonably last 5 to 11 days, but not beyond 14 days, without new evidence of the virus entering the housing unit.

    - All decisions should be documented and communicated with health officials.

Prisons, jails, and other places of detention that are not able to comply with ethical standards of quarantine and medical isolation in the COVID-19 pandemic should urgently implement strategies to release or transfer people to locations that have the capacity to meet community standards of medical care.



Solitary Confinement is defined by the U.S. Department of Justice as:
"[A]ny type of detention that involves: (1) removal from the general inmate population, whether voluntary or involuntary; (2) placement in a locked room or cell, whether alone or with another inmate; and (3) inability to leave the room or cell for the vast majority of the day, typically 22 hours or more."

WHO and CDC define **Medical Isolation** in a correctional context as:
"Confining a confirmed or suspected COVID-19 case (ideally to a single cell with solid walls and a solid door that closes), to prevent contact with others and to reduce the risk of transmission. Medical isolation ends when the individual meets pre-established clinical and/or testing criteria for release from isolation, in consultation with clinical providers and public health officials…In this context, isolation does NOT refer to punitive isolation for behavioral infractions within the custodial setting. Staff are encouraged to use the term "medical isolation" to avoid confusion.

The American Medical Association defines **Quarantine** as: the separation and restricted movement of people who were exposed to a contagious disease while awaiting the results of testing.

Amend COVID-19 Guidance & Tools developed by:

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Amend at UCSF fundamentally transforms culture inside prisons and jails to reduce their debilitating health effects. We provide a multi-year immersive program drawing on public health-oriented correctional practices from Norway and elsewhere to inspire changes in correctional cultures and create environments that can improve the health of people living and working in American correctional facilities.

Amend is currently focused on providing resources, expertise, and support to correctional systems confronting the global COVID-19 pandemic.

For more information: https://amend.us

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EXHIBIT 34

Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study

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Summary

Background Concerns regarding potential neurological complications of COVID-19 are being increasingly reported, primarily in small series. Larger studies have been limited by both geography and specialty. Comprehensive characterisation of clinical syndromes is crucial to allow rational selection and evaluation of potential therapies. The aim of this study was to investigate the breadth of complications of COVID-19 across the UK that affected the brain.

Methods During the exponential phase of the pandemic, we developed an online network of secure rapid-response case report notification portals across the spectrum of major UK neuroscience bodies, comprising the Association of British Neurologists (ABN), the British Association of Stroke Physicians (BASP), and the Royal College of Psychiatrists (RCPsych), and representing neurology, stroke, psychiatry, and intensive care. Broad clinical syndromes associated with COVID-19 were classified as a cerebrovascular event (defined as an acute ischaemic, haemorrhagic, or thrombotic vascular event involving the brain parenchyma or subarachnoid space), altered mental status (defined as an acute alteration in personality, behaviour, cognition, or consciousness), peripheral neurology (defined as involving nerve roots, peripheral nerves, neuromuscular junction, or muscle), or other (with free text boxes for those not meeting these syndromic presentations). Physicians were encouraged to report cases prospectively and we permitted recent cases to be notified retrospectively when assigned a confirmed date of admission or initial clinical assessment, allowing identification of cases that occurred before notification portals were available. Data collected were compared with the geographical, demographic, and temporal presentation of overall cases of COVID-19 as reported by UK Government public health bodies.

Findings The ABN portal was launched on April 2, 2020, the BASP portal on April 3, 2020, and the RCPsych portal on April 21, 2020. Data lock for this report was on April 26, 2020. During this period, the platforms received notification of 153 unique cases that met the clinical case definitions by clinicians in the UK, with an exponential growth in reported cases that was similar to overall COVID-19 data from UK Government public health bodies. Median patient age was 71 years (range 23–94; IQR 58–79). Complete clinical datasets were available for 125 (82%) of 153 patients. 77 (62%) of 125 patients presented with a cerebrovascular event, of whom 57 (74%) had an ischaemic stroke, nine (12%) an intracerebral haemorrhage, and one (1%) CNS vasculitis. 39 (31%) of 125 patients presented with altered mental status, comprising nine (23%) patients with unspecified encephalopathy and seven (18%) patients with encephalitis. The remaining 23 (59%) patients with altered mental status fulfilled the clinical case definitions for psychiatric diagnoses as classified by the notifying psychiatrist or neuropsychiatrist, and 21 (92%) of these were new diagnoses. Ten (43%) of 23 patients with neuropsychiatric disorders had new-onset psychosis, six (26%) had a neurocognitive (dementia-like) syndrome, and four (17%) had an affective disorder. 18 (49%) of 37 patients with altered mental status were younger than 60 years and 19 (51%) were older than 60 years, whereas 13 (18%) of 74 patients with cerebrovascular events were younger than 60 years versus 61 (82%) patients older than 60 years.

Interpretation To our knowledge, this is the first nationwide, cross-specialty surveillance study of acute neurological and psychiatric complications of COVID-19. Altered mental status was the second most common presentation, comprising encephalopathy or encephalitis and primary psychiatric diagnoses, often occurring in younger patients. This study provides valuable and timely data that are urgently needed by clinicians, researchers, and funders to inform immediate steps in COVID-19 neuroscience research and health policy.

Funding None.

Introduction

In December, 2019, WHO was notified by clinicians in Wuhan, China, of a novel and severe respiratory virus, later called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19, the disease caused by SARS-CoV-2, was recognised as a substantial global

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed on Jan 1, 2020, and May 11, 2020, with no language restrictions, using the search terms "COVID-19 or SARS-CoV2" with "neurological or psychiatric" and identified 133 publications and 371 publications, respectively. A focus on publications that reported data for the onset of new neurological or psychiatric diagnoses in hospitalised patients with confirmed or probable COVID-19 identified a more restricted subset of baseline data. From a neurological perspective, these publications included case reports or series (with less than ten patients) of stroke (six publications), encephalitis (five publications), seizures (one publication), cranial neuropathies (two publications), and posterior reversible encephalopathy syndrome (one publication). A larger series of 214 patients from Wuhan reported neurological symptoms in 78 patients. However, many of these symptoms were vague—for example, dizziness or headache—although a subset of 13 patients had a cerebrovascular diagnosis. A study from France reported patients with COVID-19-related acute respiratory distress syndrome, of whom eight had neurological manifestations, including two with strokes. We identified many publications that addressed the mental health effects of COVID-19 on the general population, health-care workers, and those with pre-existing psychiatric diagnoses. However, cases of new-onset psychiatric diagnoses in hospitalised patients with confirmed or probable COVID-19 were limited to a few case reports. In the large Wuhan study, acute psychiatric diagnoses were not described. In the French study, although a dysexecutive syndrome was reported in 14 patients and 26 were described as confused, little information was available with regard to what the psychiatric diagnoses were, and this cohort represented only the severe end of the respiratory spectrum.

Added value of this study

By working across the clinical neuroscience communities of neurology, psychiatry, stroke, and neurointensive care, we identified acute presentations of new-onset complications of COVID-19, reflecting the spectrum of the burden of disease. Ischaemic stroke was common in our cohort of 153 patients (most of whom were confirmed to have COVID-19). We identified a large group of patients with altered mental status, reflecting both neurological and psychiatric diagnoses, such as encephalitis and psychosis. Altered mental status was identified across all age groups, and many younger patients had this presentation.

Implications of all the available evidence

Our work highlights the importance of interdisciplinary work in the clinical neurosciences field in the COVID-19 era. Clinicians should be alert to the possibility of patients with COVID-19 developing these complications and, conversely, of the possibility of COVID-19 in patients presenting with acute neurological and psychiatric syndromes. These findings should direct future research to establish the role of viral neurotropism, host immune responses, and genetic factors in the development of such complications so that clinical management strategies can be developed.

public health emergency and SARS-CoV-2 was declared a pandemic on March 11, 2020. The neurological community were alerted to the high prevalence of anosmia and dysgeusia in early reports.[1,2,3] Some of these early cohorts also featured non-specific neurological symptoms, such as dizziness and headache.[1] However, severe neurological and neuropsychiatric presentations associated with COVID-19 have become increasingly apparent, including a patient with encephalitis in China in whom SARS-CoV-2 was identified in cerebrospinal fluid (CSF),[4] a patient with acute necrotising encephalopathy in Japan,[5] and cases of cerebrovascular disease.[1,6]

During other pandemics of respiratory pathogens, including severe acute respiratory syndrome, Middle East respiratory syndrome, and H1N1 influenza, there were similar reports of patients with neurological complications,[7,8] either during the acute phase, thought to reflect direct viral cytopathy or a para-infectious cytokine storm, or later as a post-infectious, probably cellular immune or antibody-mediated phenomenon, classically manifested as Guillain-Barré syndrome.[9] Additionally, occasional neuropsychiatric and psychiatric presentations have been reported in severe coronavirus infections,[10] although such presentations could reflect broader socioeconomic implications of the pandemic on mental health. These complications are relatively uncommon, but such patients are often the most severely affected, necessitating protracted intensive care admission and often resulting in poor outcomes.[7]

Most published reports on the neurological complications of COVID-19 are limited to individual cases or small case series.[1,4,5] A few studies showed the benefits of identifying patients with neurological complications across centres.[1,11] However, these studies have largely been limited to two or three hospitals and are restricted by both geography and specialty, therefore not assessing the neurological and neuropsychiatric complications of COVID-19 across the clinical spectrum of neurology, stroke or acute medicine, psychiatry, and intensive care.

Consequently, many important questions remain for neurologists and psychiatrists. How common are neurological and psychiatric complications in patients with COVID-19? What proportion of neurological and psychiatric complications affect the CNS versus the peripheral nervous system, and are novel syndromes emerging? And who is most at risk?

The breadth of early clinical presentations has not been represented in the literature, at least in part because

patients could be primarily managed by physicians with various clinical specialties, including neurologists, stroke or acute medical physicians, psychiatrists, or intensive care physicians. More comprehensive and integrated epidemiological characterisation is crucial to understanding the mechanisms that underlie these presentations, without which it will be impossible to rationally select, evaluate, and use appropriate therapies.

We aimed to collate data through a large-scale, national, dynamic, cross-specialty collaborative structure, to both inform best practice management guidelines and to direct research priorities.

Methods

Case notification

During the exponential phase of the pandemic, we developed an online network of secure rapid-response case report notification portals (CoroNerve platforms) comprising the Association of British Neurologists (ABN) Rare Diseases Ascertainment and Recruitment (RaDAR),[12] the British Association of Stroke Physicians (BASP),[13] and the Royal College of Psychiatrists (RCPsych),[14] in collaboration with the British Paediatric Neurology Association (BPNA),[15] the Neuro Anaesthesia and Critical Care Society (who used the ABN portal), the Intensive Care Society, and key stakeholders. Reporting portals for fully anonymised details were hosted on the web platforms of these collaborating professional bodies and via a novel web portal. Members of these professional organisations were emailed weekly to remind them of the surveillance programmes and were invited to notify the central CoroNerve Group at CoroNerve.com of any cases of COVID-19 associated with any of the clinical case definitions that they had seen through these portals.

Because of the clinical demands of the pandemic, we identified minimum clinical datasets that could be completed in under 5 min to reflect the crucial data required to determine the confidence in the diagnosis of COVID-19, demography, geography, and the nature of the clinical syndrome. Physicians were encouraged to report cases prospectively and we also permitted recent cases to be notified retrospectively when assigned a confirmed date of admission or initial clinical assessment, allowing identification of cases that occurred before notification portals were available. Patients were not randomly assigned. Awareness of the study and notification portals was increased through social platforms during the peak of the pandemic, including professional webinars, recorded online presentations, and social media. The ABN portal was launched on April 2, 2020, the BASP portal on April 3, 2020, and the RCPsych portal on April 21, 2020. Data lock for this report was on April 26, 2020. Given the propensity for hospitalisation with COVID-19 for older demographic groups, older patients were defined as those aged 60 years or older and younger patients as those less than 60 years old.

For a full list of participating hospitals and the number of cases they notified see the appendix (pp 2–3).

Evidence of COVID-19

Evidence of SARS-CoV-2 infection was defined as confirmed COVID-19 if PCR of respiratory samples (eg, nasal or throat swab) or CSF was positive for viral RNA or if serology was positive for anti-SARS-CoV-2 IgM or IgG. Cases were defined as probable COVID-19 if a chest radiograph or chest CT was consistent with COVID-19 but PCR and serology were negative or not done. Cases were defined as possible COVID-19 if the disease was suspected on clinical grounds by the notifying clinician but PCR, serology, and chest imaging were negative or not done.

Clinical case definitions

Broad clinical syndromes associated with COVID-19 were classified as a cerebrovascular event (defined as an acute ischaemic, haemorrhagic, or thrombotic vascular event involving the brain parenchyma or subarachnoid space), altered mental status (defined as an acute alteration in personality, behaviour, cognition, or consciousness),[16] peripheral neurology (defined as involving nerve roots, peripheral nerves, neuromuscular junction, or muscle), or other (with free text boxes for those not meeting these syndromic presentations). Data were collected on the specific clinical case definitions within these broad presentations, as follows: a cerebrovascular event (ischaemic stroke, intracerebral or subarachnoid haemorrhage, cerebral venous sinus thrombosis, or cerebral vasculitis); altered mental status (encephalopathy, encephalitis—defined as encephalopathy with evidence of inflammation in the CNS [CSF white cell count >5 cells per µL, protein >0·45 g/dL, or MRI consistent with inflammation], seizures [clinical or electroencephalographic evidence], and neuropsychiatric syndromes notified through psychiatrists or neuropsychiatrists [psychosis, neurocognitive

For more on the **central CoroNerve Group** see www.coronerve.com

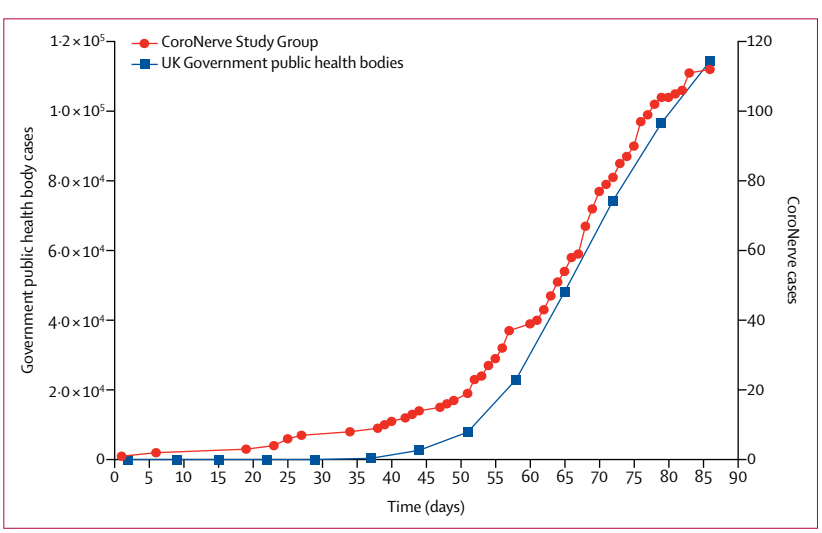

Figure 1: **Temporal distribution of the date of admission or first assessment for cases notified to the CoroNerve Study Group and those identified by UK Government public health bodies**

	All cases (n=153)	Cerebrovascular (n=77)	Altered mental status (n=39)	Peripheral (n=6)	Other (n=3)
Sex at birth					
Male	73 (48%)	44 (57%)	23 (59%)	5 (83%)	1 (33%)
Female	44 (29%)	30 (39%)	14 (36%)	0	0
Not reported	36 (24%)	3 (4%)	2 (5%)	1 (17%)	2 (67%)
Age, years					
≤20	0	0	0	0	0
21–30	4 (3%)	1 (1%)	3 (8%)	0	0
31–40	4 (3%)	1 (1%)	3 (8%)	0	0
41–50	10 (7%)	5 (6%)	4 (10%)	1 (17%)	0
51–60	17 (11%)	6 (8%)	8 (21%)	2 (33%)	1 (33%)
61–70	23 (15%)	16 (21%)	5 (13%)	2 (33%)	0
71–80	31 (20%)	23 (30%)	8 (21%)	0	0
81–90	23 (15%)	18 (23%)	5 (13%)	0	0
≥91	5 (3%)	4 (5%)	1 (3%)	0	0
Missing	36 (24%)	3 (4%)	2 (5%)	1 (17%)	2 (67%)
Median (range; IQR)	71 (23–94; 58–79)	73·5 (25–94; 64–83)	71 (23–91; 48–75)	59 (44–63; 50–62)	54 (54–54)

Data are n (%), unless otherwise indicated.

Table: **Sex and age data for notified patients**

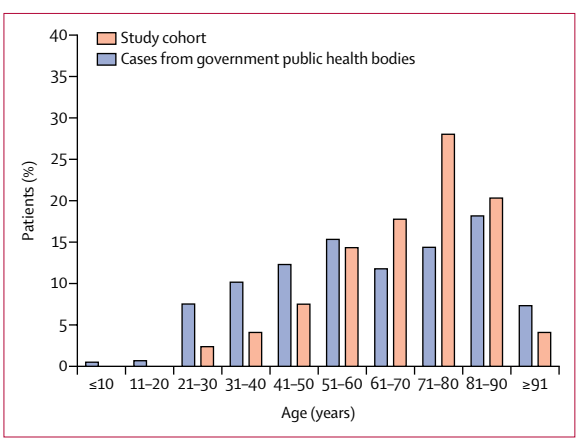

Figure 2: **Age distribution of all cases notified to the CoroNerve Study Group and national data collected by UK Government public health bodies within the first 3 weeks of CoroNerve accepting notifications**

dementia-like syndrome, personality change, catatonia, mania, anxiety or depression, chronic fatigue syndrome, and post-traumatic stress disorder]); and peripheral neurology (Guillain-Barré syndrome, Miller Fisher syndrome, brachial neuritis, myasthenia gravis, peripheral neuropathy, myopathy, myositis—defined as myopathy with evidence of inflammation [eg, by MRI or biopsy of muscle with elevated creatine kinase], and critical illness neuromyopathy).

When patients met more than one specific clinical case definition (eg, seizures and encephalitis), the underlying causal diagnosis was considered primary and complications of that diagnosis considered secondary features (eg, encephalitis would be considered primary and seizures secondary). Where there were discrepancies in classification, these were resolved through discussion with senior authors (BDM, IG, and RHT).

Additional data collection

By asking reporting physicians to submit their contact details at the time of notification (including a National Health Service email address), we established confirmation of the veracity of the data and created a log for subsequent sample collection and longitudinal follow-up studies, through linkage with existing platforms including co-recruitment into the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterisation Protocol, which was also recorded.[17] Data collected were compared with the geographical, demographic, and temporal presentation of overall cases of COVID-19 as reported by national government public health bodies representing each of the regions of the UK (Public Health England, Health Protection Scotland, Public Health Wales, and the Public Health Agency [Northern Ireland]).

The UK Health Research Authority formally confirmed this approach was compliant with regulations regarding anonymised surveillance of routine clinical practice in pandemic conditions, as initiated by the local attending clinician.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the first 3 weeks of the submission portals accepting notifications (April 2–26, 2020), the CoroNerve study platforms received notification of 153 unique cases that met the clinical case definitions by clinicians in the UK. Patients were geographically dispersed across the UK, as were overall laboratory-confirmed cases of patients with COVID-19 reported by government public health bodies during the same time period (appendix p 1). Data from the admitting medical units were available for 152 (99%) of 153 patients. 26 (17%) of 152 patients were from tertiary care hospitals, 125 (82%) were from secondary care hospitals, and one (1%) was from primary care. Overall, 75 (49%) of 153 cases were notified through the BASP portal, 53 (35%) through ABN or CoroNerve.com, and 25 (16%) through the RCPsych portal. Cases were reported retrospectively for 24 (16%) of 153 patients and the remainder were reported prospectively. The BPNA surveillance network was not available for notifications, as the portal was not live during the study period. Data on reporting physician specialty were available for 150 patients: 61 (41%) were stroke physicians, 39 (26%) were neurologists, 26 (17%) were psychiatrists or neuropsychiatrists, 23 (15%) were acute medicine or other physicians, and one (1%) was a general practitioner.

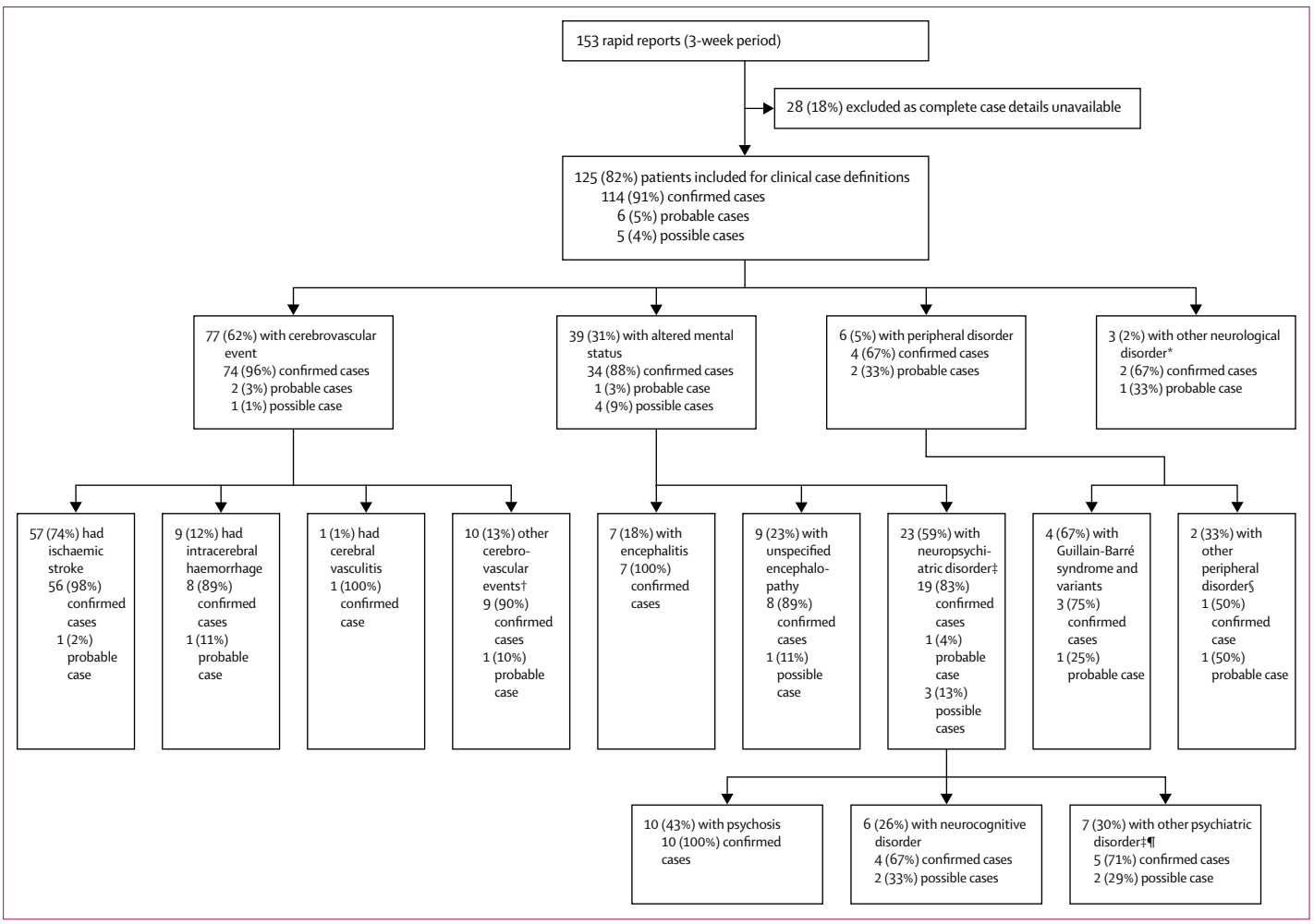

Figure 3: **Number of broad and specific clinical case definitions notified in the dataset, including evidence for severe acute respiratory syndrome coronavirus 2 within each grouping, according to the clinical case definition**

*One patient with opsoclonus-myoclonus syndrome, one patient with sixth nerve palsy, and one patient with seizures. †Two patients with cerebral venous thrombosis, two patients with transient ischaemic attack, one patient with subarachnoid haemorrhage, and five unspecified. ‡1 case with missing SARS-CoV2 data. §One patient with brachial neuritis and one patient with myasthenic crisis. ¶Three patients with depression, two patients with personality change, one patient with catatonia, and one patient with mania.

Complete clinical datasets were available for 125 (82%) of 153 patients. Dates of admission or initial clinical assessment were available for 112 (90%) of 125 patients and correlated with the national case identification data of all laboratory-confirmed patients with COVID-19 reported by government public health bodies over the same time period, reflecting the exponential phase of infection (figure 1).

Data on the sex and age of notified patients are reported in the table. Overall, the median age of 71 years (range 23–94; IQR 58–79) was similar to national data collected through UK Government public health bodies over the same time period, although for some centiles an older population could be overrepresented within the study cohort (figure 2). Data were available for sex for 117 (76%) of 153 patients as this question was not included in the original ABN RaDAR web portal, representing 28 (19%) cases, and this question was not answered in the other portals in eight (5%) cases. Therefore, data regarding sex were available for 117 (94%) of 125 patients for whom these data were requested.

114 (92%) of 125 patients with complete notification data met the criteria for confirmed SARS-CoV-2 infection, five (4%) met the criteria for probable SARS-CoV-2 infection, and five (4%) met the criteria for possible SARS-CoV-2 infection. 77 (62%) of 125 patients presented with the broad clinical syndrome of a cerebrovascular event, of whom 57 (74%) had an ischaemic stroke and nine (12%) an intracerebral haemorrhage. A clinical diagnosis of CNS vasculitis was reported in one (1%) patient with an unusual and otherwise unexplained infarct of the corpus callosum and imaging appearances suggestive of vasculitis; however, the full angiographic report and pathological confirmation were not provided (figure 3). Beyond cerebrovascular events, 39 (31%) of 125 patients presented with altered mental status,

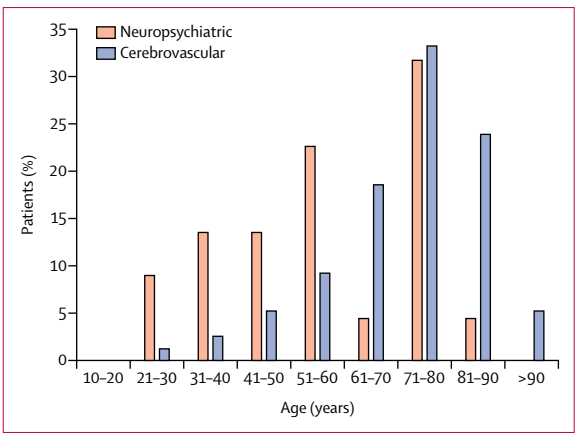

Figure 4: **Age distribution of patients identified through the CoroNerve surveillance study meeting the clinical case definitions for cerebrovascular and neuropsychiatric events**

comprising nine (23%) patients with unspecified encephalopathy and seven (18%) patients with both clinical symptoms or signs of encephalopathy and evidence of CNS inflammation meeting the clinical case definition for encephalitis. All seven patients with encephalitis met the criteria for confirmed SARS-CoV-2 infection. The remaining 23 (59%) patients with altered mental status fulfilled the clinical case definitions for psychiatric diagnoses as classified by the notifying psychiatrist or neuropsychiatrist. Only two (9%) of 23 patients had exacerbations of existing enduring mental illness. Ten (43%) of 23 patients with neuropsychiatric disorders had new-onset psychosis, six (26%) had a neurocognitive (dementia-like) syndrome, and seven (30%) had an other psychiatric disorder, including one case of catatonia and one case of mania.

Age data were available for 74 (96%) of 77 patients with cerebrovascular events and 37 (95%) of 39 patients with altered mental status. 18 (49%) of 37 patients with altered mental status were younger than 60 years and 19 (51%) were older than 60 years, whereas 13 (18%) of 74 patients with cerebrovascular events were younger than 60 years versus 61 (82%) patients older than 60 years (figure 4).

Discussion

To our knowledge, this is the first systematic, nationwide UK surveillance study of the breadth of acute complications of COVID-19 in the nervous system, undertaken through rapid mobilisation of UK professional bodies representing neurology, stroke or acute medicine, psychiatry, and intensive care. Cases notified by the professional membership of these bodies were obtained from across the UK, and an exponential rise in cases of neurological and psychiatric complications of COVID-19 occurred during the exponential rise in overall COVID-19 cases reported by UK Government public health bodies.

Future studies on neurological complications of COVID-19, particularly those assessing genetic and associated risk factors, would benefit from obtaining notification of all cases of infection admitted to every hospital as a denominator, or a cohort of COVID-19 patients without neurological or psychiatric complications as a control group. However, given the time pressure on busy clinical teams during the pandemic, we focused our notification structure on patients with neurological or psychiatric complications of infection. Cases were reported from physicians who spanned various specialties, and almost all cases met the case definition of confirmed SARS-CoV-2 infection.

Cerebrovascular events in patients with COVID-19, which have been well described elsewhere,[1,9] were also identified as a major group within our cohort. However, we identified a large proportion of cases of acute alteration in mental status, comprising neurological syndromic diagnoses such as encephalopathy and encephalitis and primary psychiatric syndromic diagnoses, such as psychosis. Although cerebrovascular events and altered mental status were identified across all age groups, our cohort confirms that cerebrovascular events predominate in older patients; however, these early data identify that acute alterations in mental status were disproportionately overrepresented in younger patients in our cohort. Our rates of neurological and psychiatric complications of COVID-19 cannot be extrapolated to mildly affected patients or patients with asymptomatic infection, especially those in the community, but give a broad national perspective on complications severe enough to require hospitalisation.

Our approach to case ascertainment has the potential for reporting bias and requires validation through detailed prospective clinicoepidemiological data collection. Plans for such studies should be developed in advance of future pandemics, so that they can be mobilised early during disease spread. A more engaged professional membership or those more used to submitting data to surveillance studies through this approach could potentially be overrepresented in our results. However, this study was the first major national investigation to use a data surveillance approach for clinicians, who notified a large proportion of our cohort (ie, BASP and RCPsych). Additionally, the present study included a priori considerations to determine the strength of the evidence for SARS-CoV-2 infection, and data collection was informed by clear clinical case definitions. Moreover, in this cohort, we conclude that this study is unlikely to have had systematic over ascertainment bias for psychiatric or neuropsychiatric presentations. 41% of cases were reported by stroke physicians, and the RCPsych web portal was launched 18 days later than the other neurological, stroke, and intensive care unit or more general portals, yet we observed a large number of psychiatric or neuropsychiatric notifications. Indeed, as many patients with COVID-19 are managed in intensive care units with sedative and paralytic medications, which can both mask and contribute to iatrogenic complications, our cohort might underrepresent the rate of neurological or

psychiatric symptoms.[18] Since we specifically identified moderate to severe complications of COVID-19 as they were reported for inpatient cases by neurologists and psychiatrists, our cohort might underrepresent patients with milder outpatient symptoms, such as reduced taste or smell. Future hypothesis testing studies building on our findings to infer causal relationships between infection and neurological or neuropsychiatric presentations should adhere to basic principles, such as the criteria for causation outlined by Bradford Hill as they pertain to pandemic respiratory infection and effects on the brain.[19]

Many cerebrovascular events were identified in our study, as reported in previous cohorts and case reports of acute COVID-19 complications.[1,20,21] The pathophysiological mechanisms that underlie cerebrovascular events in COVID-19 require further study, but there is a potential biological rationale for a vasculopathy, with a report of SARS-CoV-2 endothelitis in organs outside the cerebral vasculature[22] and cerebrovascular events,[23] in addition to coagulopathy, along with conventional stroke risk during sepsis.[9,24,25] Comprehensive studies with clear control groups, including patients hospitalised with COVID-19 but without cerebrovascular events and patients with cerebrovascular events but who do not have COVID-19, are required to address this issue.

Confirmation of the link between COVID-19 and new acute psychiatric or neuropsychiatric complications in younger patients will require detailed prospective longitudinal studies. Understanding this association will require systematic participant evaluation, characterisation of immune host responses, exploration of genetic associations, and comparison with appropriate controls (including patients hospitalised with COVID-19 who do not have acute neuropsychiatric features).

Altered mental status is common in patients admitted to hospital with severe infection, especially in those requiring intensive care management. However, this symptom typically predominates in older groups, and might reflect an unmasking of latent neurocognitive degenerative disease or multiple medical comorbidities, often in association with sepsis, hypoxia, and the requirement for polypharmacy and sedative medications. In this study, we observed a disproportionate number of neuropsychiatric presentations in younger patients and a predominance of cerebrovascular complications in older patients, which might reflect the state of health of the cerebral vasculature and associated risk factors, exacerbated by critical illness in older patients.[25] The large number of patients with altered mental status might reflect increased access to neuropsychiatry or psychiatry review for younger patients, and increased attribution of altered mental status to delirium in older patients. Nevertheless, the increased recognition of acute altered mental status in patients hospitalised with COVID-19 warrants study. The exclusion of iatrogenic factors, such as sedatives and antipsychotics, should be quantified in future modelling studies. In our study, although most psychiatric diagnoses were determined as new by the notifying psychiatrist or neuropsychiatrist, we cannot exclude the possibility that these were undiagnosed before the patient developed COVID-19.

Our study population represents a snapshot of hospitalised patients with acute neurological or psychiatric complications associated with COVID-19. Larger, ideally prospective, studies should identify the broader cohort of COVID-19 patients both in and outside hospitals, with capture–recapture analysis and health record linkage to determine clearer estimates of the prevalence of these complications and individuals at risk. Additionally, community studies are required to identify those at risk of both COVID-19 and neurological or psychiatric complications, although this strategy will require widespread serological testing.

The importance of data sharing is increasingly recognised as fundamental to facilitate rapidly responsive clinical research and is particularly crucial during an international emergency, such as the SARS-CoV-2 pandemic. The CoroNerve Study Group has been made possible by open collaboration between several UK institutions. We anticipate added value of sharing data more widely, across European and global partners, particularly in low-income and middle-income countries. The Brain Infections Global COVID-Neuro Network is supporting data collection in such countries through freely available case record forms.[26] Wide collaboration is likely to be even more important for characterising rarer or novel COVID-19-associated neurological syndromes. These enriched populations that reflect less common, but nevertheless severe, disease must be studied in close collaboration with larger surveillance efforts, such as the ISARIC Clinical Characterisation Protocol, to identify at-risk groups, determine the strength of relative risk factors, and have adequate controls for mechanistic studies.

Our nationwide, clinician-reported cohort approach provides valuable and timely information that is urgently needed by clinicians, researchers, and funders to inform the immediate next steps in COVID-19 neuroscience-related research and health policy planning. These national data begin to characterise the spectrum of neurological and neuropsychiatric complications that need to be addressed. This multidisciplinary, coordinated approach should be emulated in detailed national mechanistic studies of COVID-19 and the brain, to distinguish the role of the virus and the host inflammatory response versus the broader socioeconomic effects of the pandemic.[27]

Contributors
AV and BDM drafted the initial manuscript and the document was edited and approved by all coauthors.

Declaration of interests
AV is a Medical Research Council (MRC) PhD fellow. MAE is an Association of British Neurologists PhD fellow. MZ reports personal fees from UCB Pharma outside the submitted work. JPC received funding from the National Institute for Health Research (NIHR) Cambridge

BioMedical Research Centre during the conduct of the study. LAB reports funding from GlaxoSmithKline and Research England, outside the submitted work. AC reports personal fees from independent testimony in court on a range of neuropsychiatric topics and as a paid editor of the Journal of Neurology, Neurosurgery and Psychiatry, outside the submitted work. Additionally, AC is planning a rehabilitation trial after COVID-19, which could produce an application that might be associated with intellectual property. CS has received funding from the MRC, NIHR, The Leducq Foundation, and The Stroke Association. MRT reports grants from Motor Neurone Disease Association and My Name'5 Doddie Foundation, and personal fees from Oxford University Press, Oneworld, Karger Publishing, Orphazyme, BMJ Publishing, and GLG Consulting, outside the submitted work. TS reports consultancy for GlaxoSmithKline Ebola Vaccine programme, Siemens Diagnostics Clinical Advisory Board, Siemens Healthineers Clinical Advisory Board, and the Data Safety Monitoring Committee of the GlaxoSmithKline Study to Evaluate the Safety and Immunogenicity of a Candidate Ebola Vaccine in Children GSK3390107A (ChAd3 EBO-Z) vaccine, during the conduct of the study. Additionally, TS has a patent filed for a blood test for bacterial meningitis (GB 1606537.7; April 14, 2016). TS is supported by the European Union's Horizon 2020 research and innovation program ZikaPLAN (Preparedness Latin America Network; 734584). SLP has received funding from the MRC. IG has received funding from the NIHR. RHT reports personal fees from Eisai, GW Pharma, Sanofi, UCB Pharma, Zogenix, Bial, and Arvelle, outside the submitted work. RHT has received funding from the Academy of Medical Sciences (AMS) and Wellcome. BDM has received funding from the MRC, AMS, Wellcome, and the NIHR. BDM and TS are supported by the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections (IS-HPU-1112-10117) and the NIHR Global Health Research Group on Brain Infections (17/63/110). All other authors declare no competing interests.

Data sharing

The authors are committed to open science. The broader data from these studies will be made available at the end of the studies wherever possible, within the terms of participant consent and when not otherwise restricted by intellectual property rights or ongoing collaborative research. To avoid the possibility of identifying individual cases, detailed data are not given in the paper or appendix but are available on appropriate request to the corresponding author.

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EXHIBIT 35

Centers for Disease Control and Prevention

Coronavirus Disease 2019 (COVID-19)

Preparing for COVID-19 in Nursing Homes

Updated June 25, 2020

Print Page

Summary of Changes to the Guidance:

- Tiered recommendations to address nursing homes in different phases of COVID-19 response
- Added a recommendation to assign an individual to manage the facility's infection control program
- Added guidance about new requirements for nursing homes to report to the National Healthcare Safety Network (NHSN)
- Added a recommendation to create a plan for testing residents and healthcare personnel for SARS-CoV-2

Background

Given their congregate nature and resident population served (e.g., older adults often with underlying chronic medical conditions), nursing home populations are at high risk of being affected by respiratory pathogens like COVID-19 and other pathogens, including multidrug-resistant organisms (e.g., Carbapenemase-producing organisms, *Candida auris*). As demonstrated by the COVID-19 pandemic, a strong infection prevention and control (IPC) program is critical to protect both residents and healthcare personnel (HCP).

Facilities should assign at least one individual with training in IPC to provide on-site management of their COVID-19 prevention and response activities because of the breadth of activities for which an IPC program is responsible, including developing IPC policies and procedures, performing infection surveillance, providing competency-based training of HCP, and auditing adherence to recommended IPC practices.

The Centers for Medicare and Medicaid Services (CMS) recently issued Nursing Home Reopening Guidance for State and Local Officials that outlines criteria that could be used to determine when nursing homes could relax restrictions on visitation and group activities and when such restrictions should be reimplemented. Nursing homes should consider the current situation in their facility and community and refer to that guidance as well as direction from state and local officials when making decisions about relaxing restrictions. When relaxing any restrictions, nursing homes must **remain vigilant for COVID-19 among residents and HCP in order to prevent spread and protect residents and HCP** from severe infections, hospitalizations, and death.

This guidance has been updated and reorganized according to **core IPC practices** that should remain in place even as nursing homes resume normal practices, plus **additional strategies** depending on the stages described in the CMS Reopening Guidance or at the direction of state and local officials. This guidance is based on currently available information about COVID-19 and will be refined and updated as more information becomes available.

These recommendations supplement the CDC's Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings and are specific for nursing homes, including skilled nursing facilities.

Additional Key Resources:

- Considerations for the Public Health Response to COVID-19 in Nursing Homes
- Interim Testing in Response to Suspected or Confirmed COVID-19 in Nursing Home Residents and Healthcare Personnel

- Considerations for Performing Facility-wide SARS-CoV-2 Testing in Nursing Homes
- Considerations for Memory Care Units in Long-Term Care Facilities
- Infection Prevention and Control Assessment Tool for Nursing Homes Preparing for COVID-19

Core Practices

These practices should remain in place even as nursing homes resume normal activities.

Assign One or More Individuals with Training in Infection Control to Provide On-Site Management of the IPC Program.

- This should be a full-time role for at least one person in facilities that have more than 100 residents or that provide on-site ventilator or hemodialysis services. Smaller facilities should consider staffing the IPC program based on the resident population and facility service needs identified in the facility risk assessment.
- CDC has created an online training course that can be used to orient individuals to this role in nursing homes.

Report COVID-19 cases, facility staffing, and supply information to the National Healthcare Safety Network (NHSN) Long-term Care Facility (LTCF) COVID-19 Module weekly.

- CDC's NHSN provides long-term care facilities with a customized system to track infections and prevention process measures in a systematic way. Nursing homes can report into the four pathways of the LTCF COVID-19 Module including:
  - Resident impact and facility capacity
  - Staff and personnel impact
  - Supplies and personal protective equipment
  - Ventilator capacity and supplies
- Weekly data submission to NHSN will meet the CMS COVID-19 reporting requirements.

Educate Residents, Healthcare Personnel, and Visitors about COVID-19, Current Precautions Being Taken in the Facility, and Actions They Should Take to Protect Themselves.

- Provide information about COVID-19 (including information about signs and symptoms) and strategies for managing stress and anxiety.
- Regularly review CDC's Infection Control Guidance for Healthcare Professionals about COVID-19 for current information and ensure staff and residents are updated when this guidance changes.
- Educate and train HCP, including facility-based and consultant personnel (e.g., wound care, podiatry, barber) and volunteers who provide care or services in the facility. Including consultants is important, since they commonly provide care in multiple facilities where they can be exposed to and serve as a source of COVID-19.
  - Reinforce sick leave policies, and **remind HCP not to report to work when ill.**
  - Reinforce adherence to standard IPC measures including hand hygiene and selection and correct use of personal protective equipment (PPE). Have HCP demonstrate competency with putting on and removing PPE and monitor adherence by observing their resident care activities.
    - CDC has created training modules for front-line staff that can be used to reinforce recommended practices for preventing transmission of SARS-CoV-2 and other pathogens.
  - Educate HCP about any new policies or procedures.
- Educate residents and families on topics including information about COVID-19, actions the facility is taking to protect them and/or their loved ones, any visitor restrictions that are in place, and actions residents and families should take to protect themselves in the facility, emphasizing the importance of hand hygiene and source control.
- Have a plan and mechanism to regularly communicate with residents, families and HCP, including if cases of COVID-19 are identified among residents or HCP.

Implement Source Control Measures.

- HCP should wear a facemask at all times while they are in the facility.
  - When available, facemasks are generally preferred over cloth face coverings for HCP as facemasks offer both source control and protection for the wearer against exposure to splashes and sprays of infectious material from

others. Guidance on extended use and reuse of facemasks is available. **Cloth face coverings should NOT be worn by HCP instead of a respirator or facemask if PPE is required.**

- Residents should wear a cloth face covering or facemask (if tolerated) whenever they leave their room, including for procedures outside the facility. Cloth face coverings should not be placed on anyone who has trouble breathing, or anyone who is unconscious, incapacitated, or otherwise unable to remove the mask without assistance. In addition to the categories described above cloth face coverings should not be placed on children under 2.
- Visitors, if permitted into the facility, should wear a cloth face covering while in the facility.

Have a Plan for Visitor Restrictions.

- Send letters or emails to families reminding them not to visit when ill or if they have a known exposure to someone with COVID-19.
- Facilitate and encourage alternative methods for visitation (e.g., video conferencing) and communication with the resident

- Post signs at the entrances to the facility advising visitors to check-in with the front desk to be assessed for symptoms prior to entry.
  - Screen visitors for fever (T≥100.0ºF), symptoms consistent with COVID-19, or known exposure to someone with COVID-19. Restrict anyone with fever, symptoms, or known exposure from entering the facility.
- Ask visitors to inform the facility if they develop fever or symptoms consistent with COVID-19 within 14 days of visiting the facility.
- Have a plan for when the facility will implement additional restrictions, ranging from limiting the number of visitors and allowing visitation only during select hours or in select locations to restricting all visitors, except for compassionate care reasons (see below).

Create a Plan for Testing Residents and Healthcare Personnel for SARS-CoV-2.

- Testing for SARS-CoV-2, the virus that causes COVID-19, in respiratory specimens can detect current infections (referred to here as viral testing or test) among residents and HCP in nursing homes.
- The plan should align with state and federal requirements for testing residents and HCP for SARS-CoV-2 and address:
  - Triggers for performing testing (e.g., a resident or HCP with symptoms consistent with COVID-19, response to a resident or HCP with COVID-19 in the facility, routine surveillance)
  - Access to tests capable of detecting the virus (e.g., polymerase chain reaction) and an arrangement with laboratories to process tests
    - Antibody test results should not be used to diagnose someone with an active SARS-CoV-2 infection and should not be used to inform IPC action.
  - Process for and capacity to perform SARS-CoV-2 testing of all residents and HCP
  - A procedure for addressing residents or HCP who decline or are unable to be tested (e.g., maintaining Transmission-Based Precautions until symptom-based criteria are met for a symptomatic resident who refuses testing)
- Additional information about testing of residents and HCP is available:
  - CDC Strategy for COVID-19 Testing Nursing Homes.
  - Considerations for Performing Facility-wide SARS-CoV-2 Testing in Nursing Homes

Evaluate and Manage Healthcare Personnel.

- Implement sick leave policies that are non-punitive, flexible, and consistent with public health policies that support HCP to stay home when ill.
- Create an inventory of all volunteers and personnel who provide care in the facility. Use that inventory to determine which personnel are non-essential and whose services can be delayed if such restrictions are necessary to prevent or control transmission.
- As part of routine practice, ask HCP (including consultant personnel and ancillary staff such as environmental and dietary services) to regularly monitor themselves for fever and symptoms consistent with COVID-19.
  - Remind HCP to stay home when they are ill.

- If HCP develop fever (T≥100.0°F) or symptoms consistent with COVID-19 while at work they should inform their supervisor and leave the workplace. Have a plan for how to respond to HCP with COVID-19 who worked while ill (e.g., identifying and performing a risk assessment for exposed residents and co-workers).
- HCP with suspected COVID-19 should be prioritized for testing.

- Screen all HCP at the beginning of their shift for fever and symptoms of COVID-19.
  - **Actively take their temperature*** and document absence of symptoms consistent with COVID-19. If they are ill, have them keep their cloth face covering or facemask on and leave the workplace.
  - *Fever is either measured temperature >100.0°F or subjective fever. Note that fever may be intermittent or may not be present in some individuals, such as those who are elderly, immunosuppressed, or taking certain medications (e.g., NSAIDs). Clinical judgement should be used to guide testing of individuals in such situations.
  - HCP who work in multiple locations may pose higher risk and should be encouraged to tell facilities if they have had exposure to other facilities with recognized COVID-19 cases.
- Develop (or review existing) plans to mitigate staffing shortages from illness or absenteeism.
  - CDC has created guidance to assist facilities with mitigating staffing shortages.
  - For guidance on when HCP with suspected or confirmed COVID-19 may return to work, refer to Criteria for Return to Work for Healthcare Personnel with Confirmed or Suspected COVID-19 (Interim Guidance)

Provide Supplies Necessary to Adhere to Recommended Infection Prevention and Control Practices.

- Hand Hygiene Supplies:
  - Put alcohol-based hand sanitizer with 60-95% alcohol in every resident room (ideally both inside and outside of the room) and other resident care and common areas (e.g., outside dining hall, in therapy gym). Unless hands are visibly soiled, an alcohol-based hand sanitizer is preferred over soap and water in most clinical situations.
  - Make sure that sinks are well-stocked with soap and paper towels for handwashing.
- Respiratory Hygiene and Cough Etiquette:
  - Make tissues and trash cans available in common areas and resident rooms for respiratory hygiene and cough etiquette and source control.
- Personal Protective Equipment (PPE):
  - Perform and maintain an inventory of PPE in the facility.
    - Identify health department or healthcare coalition contacts for getting assistance during PPE shortages. The Supplies and Personal Protective Equipment pathway in the NHSN LTCF COVID-19 Module can be used to indicate critical PPE shortages (i.e., less than one week supply remaining despite use of PPE conservation strategies).
    - Monitor daily PPE use to identify when supplies will run low; use the PPE burn rate calculator or other tools.
  - Make necessary PPE available in areas where resident care is provided.
    - Consider designating staff responsible for stewarding those supplies and monitoring and providing just-in-time feedback promoting appropriate use by staff.
    - Facilities should have supplies of facemasks, respirators (if available and the facility has a respiratory protection program with trained, medically cleared, and fit-tested HCP), gowns, gloves, and eye protection (i.e., face shield or goggles).
  - Position a trash can near the exit inside the resident room to make it easy for staff to discard PPE prior to exiting the room or before providing care for another resident in the same room.
  - Implement strategies to optimize current PPE supply ***even before shortages occur***, including bundling resident care and treatment activities to minimize entries into resident rooms. Additional strategies might include:
    - Extended use of respirators, facemasks, and eye protection, which refers to the practice of wearing the same respirator or facemask and eye protection for the care of more than one resident (e.g., for an entire shift).
      - Care must be taken to **avoid touching the respirator, facemask, or eye protection**. If this must occur (e.g., to adjust or reposition PPE), HCP should perform hand hygiene immediately after touching PPE to prevent contaminating themselves or others.
    - Prioritizing gowns for activities where splashes and sprays are anticipated (including aerosol-generating procedures) and high-contact resident care activities that provide opportunities for transfer of pathogens to hands and clothing of HCP.
      - **If extended use of gowns is implemented as part of crisis strategies, the same gown should not be worn when caring for different residents unless it is for the care of residents with confirmed COVID-19 who are**

cohorted in the same area of the facility and these residents are not known to have any co-infections (e.g., *Clostridioides difficile*)

- Implement a process for decontamination and reuse of PPE such as face shields and goggles.
- Facilities should continue to assess PPE supply and current situation to determine when a return to standard practices can be considered.

- Implement a respiratory protection program that is compliant with the OSHA respiratory protection standard for employees if not already in place. The program should include medical evaluations, training, and fit testing.
- Environmental Cleaning and Disinfection:
  - Develop a schedule for regular cleaning and disinfection of shared equipment, frequently touched surfaces in resident rooms and common areas;
  - Ensure EPA-registered, hospital-grade disinfectants are available to allow for frequent cleaning of high-touch surfaces and shared resident care equipment.
    - Use an EPA-registered disinfectant from List N on the EPA website to disinfect surfaces that might be contaminated with SARS-CoV-2. Ensure HCP are appropriately trained on its use.

Identify Space in the Facility that Could be Dedicated to Monitor and Care for Residents with COVID-19.

- Identify space in the facility that could be dedicated to care for residents with confirmed COVID-19. This could be a dedicated floor, unit, or wing in the facility or a group of rooms at the end of the unit that will be used to cohort residents with COVID-19.
  - Identify HCP who will be assigned to work only on the COVID-19 care unit when it is in use.
- Have a plan for how residents in the facility who develop COVID-19 will be handled (e.g., transfer to single room, implement use of Transmission-Based Precautions, prioritize for testing, transfer to COVID-19 unit if positive).
  - Residents in the facility who develop symptoms consistent with COVID-19 could be moved to a single room pending results of SARS-CoV-2 testing. They should not be placed in a room with a new admission nor should they be moved to the COVID-19 care unit unless they are confirmed to have COVID-19 by testing. While awaiting results of testing, HCP should wear an N95 or higher-level respirator (or facemask if a respirator is not available), eye protection (i.e., goggles or a disposable face shield that covers the front and sides of the face), gloves, and gown when caring for these residents. **Cloth face coverings are not considered PPE and should only be worn by HCP for source control, not when PPE is indicated.**
- Have a plan for how roommates, other residents, and HCP who may have been exposed to an individual with COVID-19 will be handled (e.g., monitor closely, avoid placing unexposed residents into a shared space with them).
- Additional information about cohorting residents and establishing a designated COVID-19 care unit is available in the Considerations for the Public Health Response to COVID-19 in Nursing Homes

Create a Plan for Managing New Admissions and Readmissions Whose COVID-19 Status is Unknown.

- Depending on the prevalence of COVID-19 in the community, this might include placing the resident in a single-person room or in a separate observation area so the resident can be monitored for evidence of COVID-19. HCP should wear an N95 or higher-level respirator (or facemask if a respirator is not available), eye protection (i.e., goggles or a disposable face shield that covers the front and sides of the face), gloves, and gown when caring for these residents. Residents can be transferred out of the observation area to the main facility if they remain afebrile and without symptoms for 14 days after their admission. Testing at the end of this period can be considered to increase certainty that the resident is not infected.

Evaluate and Manage Residents with Symptoms of COVID-19.

- Ask residents to report if they feel feverish or have symptoms consistent with COVID-19.
- Actively monitor all residents upon admission and at least daily for fever (T≥100.0°F) and symptoms consistent with COVID-19. Ideally, include an assessment of oxygen saturation via pulse oximetry. If residents have fever or symptoms consistent with COVID-19, implement Transmission-Based Precautions as described below.
  - Older adults with COVID-19 may not show common symptoms such as fever or respiratory symptoms. Less common symptoms can include new or worsening malaise, headache, or new dizziness, nausea, vomiting, diarrhea, loss of taste or smell. Additionally, more than two temperatures >99.0°F might also be a sign of fever in this population. Identification of these symptoms should prompt isolation and further evaluation for COVID-19.

- The health department should be notified about residents or HCP with suspected or confirmed COVID-19, residents with severe respiratory infection resulting in hospitalization or death, or ≥ 3 residents or HCP with new-onset respiratory symptoms within 72 hours of each other.
    - Contact information for the healthcare-associated infections program in each state health department is available here: https://www.cdc.gov/hai/state-based/index.html
    - Refer to CDC resources for performing respiratory infection surveillance in long-term care facilities during an outbreak.
- Information about the clinical presentation and course of patients with COVID-19 is described in the Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease 2019 (COVID-19). CDC has also developed guidance on Evaluating and Reporting Persons Under Investigation (PUI).
- **If COVID-19 is suspected, based on evaluation of the resident or prevalence of COVID-19 in the community,** follow the Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings. **This guidance should be implemented immediately once COVID-19 is suspected**
    - Residents with suspected COVID-19 should be prioritized for testing.
    - Residents with known or suspected COVID-19 do not need to be placed into an airborne infection isolation room (AIIR) but should ideally be placed in a private room with their own bathroom.
        - Residents with COVID-19 should, ideally, be cared for in a dedicated unit or section of the facility with dedicated HCP (see section on Dedicating Space).
        - As roommates of residents with COVID-19 might already be exposed, it is generally not recommended to place them with another roommate until 14 days after their exposure, assuming they have not developed symptoms or had a positive test.
    - Residents with known or suspected COVID-19 should be cared for using all recommended PPE, which includes use of an N95 or higher-level respirator (or facemask if a respirator is not available), eye protection (i.e., goggles or a disposable face shield that covers the front and sides of the face), gloves, and gown. **Cloth face coverings are not considered PPE and should not be worn when PPE is indicated.**
    - Increase monitoring of ill residents, including assessment of symptoms, vital signs, oxygen saturation via pulse oximetry, and respiratory exam, to at least 3 times daily to identify and quickly manage serious infection.
        - Consider increasing monitoring of asymptomatic residents from daily to every shift to more rapidly detect any with new symptoms.
    - If a resident requires a higher level of care or the facility cannot fully implement all recommended infection control precautions, the resident should be transferred to another facility that is capable of implementation**. Transport personnel and the receiving facility should be notified about the suspected diagnosis prior to transfer**.
        - While awaiting transfer, residents should be separated from others (e.g., in a private room with the door closed) and should wear a cloth face covering or facemask (if tolerated) when others are in the room and during transport.
        - All recommended PPE should be used by healthcare personnel when coming in contact with the resident.
    - Because of the higher risk of unrecognized infection among residents, universal use of all recommended PPE for the care of all residents on the affected unit (or facility-wide depending on the situation) is recommended when even a single case among residents or HCP is newly identified in the facility; this could also be considered when there is sustained transmission in the community. The health department can assist with decisions about testing of asymptomatic residents.
    - For decisions on removing residents who have had COVID-19 from Transmission-Based Precautions refer to the Interim Guidance for Discontinuation of Transmission-Based Precautions and Disposition of Hospitalized Patients with COVID-19

Additional Strategies Depending on the Facility's Reopening Status

These strategies will depend on the stages described in the CMS Reopening Guidance or the direction of state and local officials.

Implement Social Distancing Measures

- Implement aggressive social distancing measures (remaining at least 6 feet apart from others):
    - Cancel communal dining and group activities, such as internal and external activities.
    - Remind residents to practice social distancing, use a cloth face covering (if tolerated), and perform hand hygiene

- Remind residents to practice social distancing, wear a cloth face covering (if tolerated), and perform hand hygiene.
- Remind HCP to practice social distancing and wear a facemask (for source control) when in break rooms or common areas.

- Considerations when restrictions are being relaxed include:
  - Allowing communal dining and group activities for residents without COVID-19, including those who have fully recovered while maintaining social distancing, source control measures, and limiting the numbers of residents who participate.
  - Allowing for safe, socially distanced outdoor excursions for residents without COVID-19, including those who have fully recovered. Planning for such excursions should address:
    - Use of cloth face covering for residents and facemask by staff (for source control) while they are outside
    - Potential need for additional PPE by staff accompanying residents
    - Rotating schedule to ensure all residents will have an opportunity if desired, but that does not fully disrupt other resident care activities by staff
    - Defining times for outdoor activities so families could plan around the opportunity to see their loved ones

Implement Visitor Restrictions

- Restrict all visitation to their facilities except for certain compassionate care reasons, such as end-of-life situations.
  - Send letters or emails to families advising them that no visitors will be allowed in the facility except for certain compassionate care situations, such as end of life situations.
  - Use of alternative methods for visitation (e.g., video conferencing) should be facilitated by the facility.
  - Post signs at the entrances to the facility advising that no visitors may enter the facility.
  - Decisions about visitation for compassionate care situations should be made on a case-by-case basis, which should include careful screening of the visitor for fever or symptoms consistent with COVID-19. Those with symptoms should not be permitted to enter the facility. Any visitors that are permitted must wear a cloth face covering while in the building and restrict their visit to the resident's room or other location designated by the facility. They should also be reminded to frequently perform hand hygiene.

- Considerations for visitation when restrictions are being relaxed include:
  - Permit visitation only during select hours and limit the number of visitors per resident (e.g., no more than 2 visitors at one time).
  - Schedule visitation in advance to enable continued social distancing.
  - Restrict visitation to the resident's room or another designated location at the facility (e.g., outside).

Healthcare Personnel Monitoring and Restrictions:

- Restrict non-essential healthcare personnel, such as those providing elective consultations, personnel providing non-essential services (e.g., barber, hair stylist), and volunteers from entering the building.
  - Consider implementing telehealth to offer remote access to care activities.

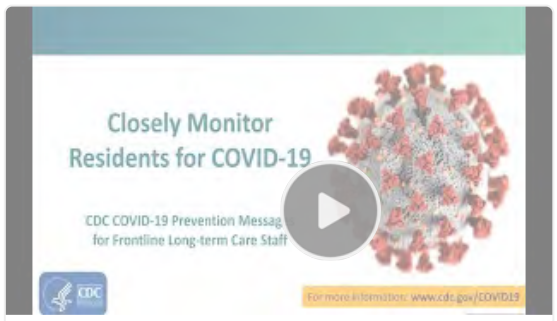
Definitions:

- **Healthcare Personnel (HCP)**: HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel).
- **Source Control**: Use of a cloth face covering or facemask to cover a person's mouth and nose to prevent spread of respiratory secretions when they are talking, sneezing, or coughing. Facemasks and cloth face coverings should not be placed on children under age 2, anyone who has trouble breathing, or anyone who is unconscious, incapacitated, or otherwise unable to remove the mask without assistance.
- **Cloth face covering**: Textile (cloth) covers that are intended to keep the person wearing one from spreading respiratory secretions when talking, sneezing, or coughing. They are not PPE and it is uncertain whether cloth face coverings protect the wearer. Guidance on design, use, and maintenance of cloth face coverings is available.

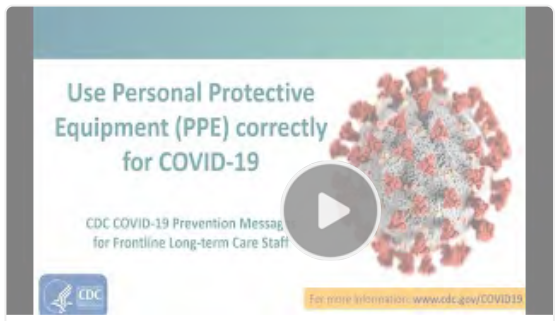
- **Facemask**: Facemasks are PPE and are often referred to as surgical masks or procedure masks. Use facemasks according to product labeling and local, state, and federal requirements. FDA-cleared surgical masks are designed to protect against splashes and sprays and are prioritized for use when such exposures are anticipated, including surgical procedures. Facemasks that are not regulated by FDA, such as some procedure masks, which are typically used for isolation purposes, may not provide protection against splashes and sprays.
- **Respirator:** A respirator is a personal protective device that is worn on the face, covers at least the nose and mouth, and is used to reduce the wearer's risk of inhaling hazardous airborne particles (including dust particles and infectious agents), gases, or vapors. Respirators are certified by the CDC/NIOSH, including those intended for use in healthcare.

Webinar Series - COVID-19 Prevention Messages for Long Term Care Staff

Clean Hands - Combat COVID-19



Closely Monitor Residents for COVID-19



PPE Lessons

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Additional Resources

Sample Notification Letter to Residents and Families: COVID-19 Transmission Identified PDF | DOC

Long-term Care Facility Letter [1 page] to Residents, Families, Friends and Volunteers

CMS Emergency Preparedness & Response Operations

Supporting Your Loved One in a Long-Term Care Facility [472 KB, 1 page]

Infection Prevention Success Stories

Applying COVID-19 Infection Prevention and Control Strategies in Nursing Homes (Recorded Webinar)

Page last reviewed: June 22, 2020

COVID-2019 Menu

- Coronavirus Home
- Your Health
- Community, Work & School
- Healthcare Workers
- Laboratories
- Health Departments
- Cases, Data & Surveillance
- More Resources

EXHIBIT 36

Centers for Disease Control and Prevention

Coronavirus Disease 2019 (COVID-19)

People with Developmental and Behavioral Disorders

Updated May 27, 2020

Print Page

Developmental and behavioral disorders are a group of conditions due to an impairment in physical, learning, language, or behavior areas. These conditions begin during the developmental period, may affect day-to-day functioning, and usually last throughout a person's lifetime.[1]

Some developmental and behavioral disorders include:

- Attention Deficit Hyperactivity Disorder (ADHD)
- Autism
- Cerebral Palsy
- Fetal Alcohol Spectrum Disorders (FASDs)
- Fragile X
- Intellectual Disability
- Learning Disorder
- Tourette Syndrome

What do people with developmental and behavioral disorders need to know about COVID-19?

Know who is at risk for severe illness from COVID-19

Most people with developmental or behavioral disorders are not naturally at higher risk for becoming infected with or having severe illness from novel coronavirus (COVID-19). However, people with developmental or behavioral disorders who have serious underlying medical conditions may be at risk of serious illness. Some people with developmental or behavioral disorders may have difficulties accessing information, understanding or practicing preventative measures, and communicating symptoms of illness.

Know how to protect yourself and others

There is currently no specific, Food and Drug Administration (FDA)-approved treatment for COVID-19, and there is currently no vaccine to prevent COVID-19. Treatment is currently supportive. Therefore, the best way to prevent illness is to avoid being exposed to this virus. Advice on preparation for COVID-19 and prevention of exposure to COVID-19 is available.

Continue with your routine care

- Don't stop any medications or change your treatment plan without talking to your healthcare provider.
- Discuss any concerns about your treatment with your healthcare provider.
- Ensure that you are obtaining the tests ordered by your healthcare provider.
- Continue to get your routine immunizations.
- Talk to your healthcare provider, insurer, and pharmacist about creating an emergency supply of prescription medications. Make sure that you have at least 30 days of prescription and over-the-counter medications and supplies on hand in case you need to stay home for a long time. Ask your healthcare provider if it is possible to obtain a 90-day supply of your prescription medications.

- Make or update care plans or an emergency notebook. They typically include important information about a person's medical conditions, how to manage those conditions, how to contact healthcare providers and therapists, allergies, information on medications (names, dosages, and administration instructions), preferences (food and other), and daily routines and activities. This may help you receive consistent care if your Direct Service Providers or family members are unavailable.

> Related: Guidance for Direct Service Providers, Caregivers, Parents, and People with Developmental and Behavioral Disorders

Know how to manage stress and cope during the pandemic

It is natural to feel concerned or stressed as more cases of COVID-19 are discovered and our communities take action to slow the spread of disease. Taking care of yourself, your friends, and your family can help you cope with stress.

Ways to cope with stress

- **Take breaks from watching, reading, or listening to news stories**, including social media. Hearing about the pandemic repeatedly can be upsetting.
- **Take care of your body**.
  - Take deep breaths, stretch, or meditate.
  - Try to eat healthy, well-balanced meals.
  - Exercise regularly, get plenty of sleep.
  - Avoid alcohol and drugs .
- **Make time to unwind**. Try to do some activities you enjoy.
- **Connect with others**. Talk with people you trust about your concerns and how you are feeling.

Click here for information on how to take steps to help yourself cope with stress and anxiety.

Take care of your mental health

Anxiety, depression, and other mental health conditions can be more common in people with some developmental and behavioral disorders. If you are being treated for a mental health condition it is important to continue any therapies or medications.

Look out for these common signs of distress:

- Feelings of numbness, disbelief, confusion, anxiety, or fear
- Changes in appetite, energy, and activity levels
- Difficulty concentrating
- Difficulty sleeping or nightmares and upsetting thoughts and images
- Physical reactions, such as headaches, body pains, stomach problems, and skin rashes
- Worsening of chronic health problems
- Anger or short temper
- Increased use of alcohol, tobacco, or other drugs

If you experience these feelings or behaviors for several days in a row and are unable to carry out normal responsibilities because of them, call your healthcare provider or use the resources below to get help. If you are feeling overwhelmed with emotions like sadness, depression, anxiety, or thoughts of hurting or killing yourself or others:

- Call 911 if you feel like you want to harm yourself or others.
- Visit the Disaster Distress Helpline , call 1-800-985-5990, or text TalkWithUs to 66746.
- Visit the National Domestic Violence Hotline or call 1-800-799-7233 and TTY 1-800-787-3224.
- Visit the National Suicide Prevention Lifeline or call 1-800-273-8255

- Visit the National Suicide Prevention Lifeline or call 1-800-273-8255.

During this pandemic, it is critical that you recognize what stress looks like, take steps to build your resilience and cope with stress, and know where to go if you need help.

More Information

Children and Youth with Special Healthcare Needs

People with Disabilities

Page last reviewed: May 27, 2020

COVID-2019 Menu

- Coronavirus Home
- Your Health
- Community, Work & School
- Healthcare Workers
- Laboratories
- Health Departments
- Cases, Data & Surveillance
- More Resources