"What Were You Before the War?"

Repurposing Psychiatry During the COVID-19 Pandemic

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Back home, when I'd tell people what I do for a living, they'd think, "Well, now, that figures." But over here, it's a big, big mystery. So, I guess I've changed some.

—Captain Miller, *Saving Private Ryan*

COVID-19, a Health Care Challenge Without Precedent in Modern Times

We are in the midst of one of the most disruptive public health events of all time. The rapidity of viral contagion, severity of illness presentation, and lack of effective means to vaccinate against or treat coronavirus disease 2019 (COVID-19) have forced governments and institutions to refocus priorities. Social distancing and case identification have quickly shifted toward suppression, but nonpharmacologic interventions are no longer sufficient to stem the tide.[1] First responders and health care workers are now themselves succumbing to the illness. The uncertainty has led to an avalanche of economic consequences and reactive social behaviors unlike anything seen since World War II.

The pipeline from treatment discovery to implementation in clinical practice takes years, if not decades.[2] Under normal circumstances, we have the luxury of years to plan and conduct treatment research. However, the game changes considerably in the context of a pandemic. Most of us are scrambling to respond to increasingly restrictive university policies on allowable research activities that consider psychiatric research "nonessential." During wartime, though, repurposing of both physical and human resources is necessary.

This is our war too as psychiatrists; those thinking that their role in the pandemic will be limited are mistaken. Our skillset as clinicians and researchers is needed, both in helping to identify and manage the negative mental health consequences of the pandemic and in battling the virus itself. Much like Captain Miller, a character played by Tom Hanks in the film *Saving Private Ryan*, we must repurpose our skills and resources—adapting to support the war effort. And the resources we bring to bear are needed now more than ever in the fight against COVID-19.

Adapting and Continuing Our Mental Health Research: Digital Tools for Fully Remote Studies

The pandemic calls for minimizing face-to-face contact, so mental health, including clinical research, needs to quickly adapt to "action at a distance." We need to immediately reassess our ongoing studies: can they still recruit, and can they still assess and safely treat existing participants? For most mental health research, the answer is yes. Psychiatry was among the first specialties to adopt telemedicine as a viable part of our care delivery system in the 1950s, out of pragmatism to address workforce shortages in clinical care as well as in medical education.[3] Digital tools are increasingly used in psychiatric clinical trials to screen and consent participants, collect data, and, in many cases, intervene remotely.[4] These tools minimize face-to-face contact with vulnerable populations, without compromising care or methodological rigor. And psychiatry has important knowledge and infrastructure to contribute to pandemic efforts. Implementing digital strategies commonly used in psychiatric care and research across COVID-19 research efforts will help keep participants and staff safe, but also could importantly expedite real-world testing of promising treatments.

Repurposing Clinical Skills: Clinicians and Clinical Researchers as a Lifeline

As noted above, institutions may deem mental health clinicians and psychiatric research functions as nonessential during a pandemic. Yet just the opposite is the case: clinicians, highly developed clinical research infrastructure, and skilled research staff all present an opportunity for moving innovative clinical approaches into service. We have an obligation to address the mental health impact of suppression efforts, economic hardship, and limited access to basic human needs during this time. Our patients may be most vulnerable to both the negative health effects of COVID-19 and the mental health impact of public health efforts to contain its spread. Living with a mental illness increases the odds of having comorbid medical conditions like diabetes and cardiovascular disease, elevating the risk for serious complications from COVID-19. But no one will escape the emotional toll of suppression efforts.

The effects of social isolation on mental and physical health outcomes, especially in vulnerable populations like older adults and children, are well established.[5] In fact, one

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of the most important contributors to all-cause mortality in older adults is social isolation.[6] As well, prolonged exposure to an environment of uncertainty and fear has lasting negative effects on mental health across the lifespan. For example, posttraumatic stress scores in children who were quarantined during the 2003 severe acute respiratory syndrome (SARS) outbreak were 4 times higher than in those who were not quarantined.[7] Providing simple interventions like rapid, patient-focused communication and encouraging voluntary preventive efforts to limit contagion can reduce the long-term psychological effects of social isolation.[8]

As healer-scientists with a unique understanding of how stress and isolation compromise immune functioning, we can help. Clinical research funding affords the opportunity, and therefore the responsibility, to connect with patients in unconventional ways—whether or not they are currently participants in our studies. Rapid procedural modifications during a pandemic allow for immediate implementation and testing of creative alternatives to traditional in-person visits. As a result, we're able to intervene now in ways that are not currently reimbursable in the existing fee-for-service structure of our health care system. For example, a phone contact to conduct a routine clinical research assessment provides an opportunity not only for connection but also for conducting critical problem-solving, treatment planning, and linkage to resources.

Telling Our Patients' Stories: Research Opportunities

We have an obligation to chronicle this extraordinary threat and its effects on mental health. If we do not measure the impacts of COVID-19 on mental health, it will be an unconscionable missed opportunity. How are people with mental illness coping? What is their reaction to isolation, uncertainty, and lack of access to needed care? What strategies are working? We need to embed these quantitative and qualitative questions into our ongoing research—now.

We also have an unprecedented opportunity to extend our reach into the communities in which we live and work, moving from the role of neutral observer to one of engaged contributor. Supporting our participants and their health care providers in this way is the right thing to do and strengthens community partnerships to the benefit of future research efforts. Doing so eases the impact of public health disasters like pandemics while we study them.

Repurposing Treatments: Psychiatric Drugs as Antiviral Therapies and Psychiatrists as Virus-Fighters

Drug repositioning is a relatively recent strategy for facilitating, and reducing costs of, drug discovery and development.[9] In the field of psychiatry, however, psychopharmacology owes its entire existence to biochemical repurposing efforts beginning in the late 1800s.[10] In fact, the subsequent reconceptualization of mental disorders as biological conditions in the 1940s and 1950s[11] can be linked to the discovery of the antitubercular effects of hydrazine derivatives, which were also observed to have mood-elevating properties.[12]

Psychiatric drugs may have important antiviral and immune modulatory effects.[13] With rapid testing, we may be able to repurpose some of these therapies that are inexpensive and already have known safety profiles. With no time to lose in the pandemic, the repurposing of known drugs is the most expeditious path toward treatments to reduce the death toll. Accordingly, the World Health Organization has launched SOLIDARITY, a global megatrial to test effectiveness of existing treatments with the most promising antiviral effects.[14] Meanwhile, a recent COVID-19 protein-pathway study reported 69 US Food and Drug Administration–approved drugs targeting those pathways as potential therapies, several of which are commonly used in the treatment of psychiatric disorders.[13]

For example, mounting evidence attributes COVID-19–related pulmonary and cardiac injury to cytokine storm syndrome,[15] suggesting treatment targets that minimize immune response. Many commonly used antidepressant medications have activity at the sigma-1 receptor (S1R). Mechanistically, S1R activation dampens cellular stress (through inhibiting activity of the endoplasmic reticulum stress sensor, IRE1) and restricts cytokine expression without inhibiting classical inflammatory signaling pathways.[16] S1R agonists have cardioprotective effects in rodents[17] and modulate inflammatory response, enhancing survival in preclinical models of sepsis.[16] Since IRE1 activity induces autophagy during coronavirus infection,[18] inhibition of IRE1 activity by S1R may also have potential to interfere directly with virus activity. Similar considerations pertain to other commonly used psychotropic drugs with other relevant mechanisms of action.

A recent *JAMA* editorial recommended the repurposing of clinical researchers to find treatments for COVID-19.[19] We have learned from previous experience that the time to start randomized clinical trials is during the outbreak, not after.[20] There are currently almost 500 ongoing trials of drugs, but thousands are needed, and in short order. Across the United States (and the world), there are highly expert clinical trial teams led by psychiatrists with skills and infrastructure to rapidly trial treatments. While our critical care skills may be lacking, our abilities to recruit, screen, manage, and provide drug and psychosocial interventions to patients are as good as in any field. Given the restrictions on face-to-face contact, these trials must be as pragmatic and fully remote as possible, another skill set psychiatric researchers can contribute. Our extensive knowledge of psychopharmacology—of both therapeutic effects and safety and tolerability profiles—as well as comfort in prescribing these agents to patients will be needed. Finally, reports of neurologic sequelae from COVID-19 infection suggest that the virus can enter the central nervous system, having acute effects on smell and taste.[21] These and other neuropsychiatric symptoms may be early warning signs of centrally mediated cardiorespiratory compromise.[22] For these reasons, psychiatric researchers will need to be engaged in studying both the acute and long-term neuropsychiatric effects of the infection.

Slowly, we are beginning to see examples of repurposing of infrastructure for much-needed medical equipment. Yesterday, General Motors workers were making cars, and Dyson was making vacuum cleaners. Today, they are making ventilators. Clinical research must do the same. We can't expect successful COVID-19 treatment research without repurposing existing clinical trial infrastructure. In other words, we won't just be repurposing drugs to fight COVID-19, we will also need to repurpose the field of clinical research in psychiatry.

Recommendations During the COVID-19 Outbreak

1. **Implement technology to reduce risk.** Researchers can minimize face-to-face contact with participants by utilizing digital tools, such as shifting to electronic informed consent[23] and digital HIPAA-compliant tools like e-mailed surveys or telehealth assessments. Virtual study visits, borrowing from telepsychiatry methods, will allow for better observation and care of infected individuals while protecting care providers and researchers.
2. **Shift unused research platforms to support COVID-19 research.** We can rapidly engage colleagues conducting treatment research, repurpose existing remote networks and research platforms, and reassign staff currently sidelined from current work due to the pandemic.
3. **Repurpose our skills for recruiting, enrolling, and evaluating study participants.** Psychiatric researchers can do more than observe. We are uniquely positioned not just to study the psychosocial and psychiatric health impacts of this pandemic but also to evaluate the short- and long-term neuropsychiatric effects of the illness.
4. **Repurpose our drugs as potential treatments.** Several potential treatments for COVID-19 are psychiatric drugs, and psychiatrists and their research teams should be part of the trialing of these drugs, particularly in outpatient settings.

The Goal: A Clinical Research Workforce With Immediate and Long-Term Impact

COVID-19 will not be the last disruption that affects quotidian life, and we need to learn from it.[24] Clinical research can adapt and ultimately improve by implementing technology and creatively repurposing existing resources. These adaptations will not only allow critical research to continue but also expand it to measure effects of COVID-19, to inform future public health events like pandemics, all while providing timely patient-focused impact for our participants. National Institutes of Health and other funders should provide administrative supplements and notifications that encourage researchers to (1) go fully remote; (2) assess the mental health impact of COVID-19; (3) prioritize repurposing of psychiatric human and pharmacologic resources for COVID-19 research efforts; and (4) continue working, leveraging the unique clinical research resources in psychiatry to help as many people as possible through the crisis.

We arrived at these ideas from a rapid, informal sharing of information and ideas with US and Canadian colleagues. We acknowledge and thank these colleagues, and we invite all to participate in new forums for discussing how psychiatric expertise can be optimally used in COVID-19 research efforts. Please share ideas at our websites, www.mhealth.wustl.edu and https://www.healthtech.pitt.edu/index.php, so that we can all apply best practices for repurposing resources in these disruptive times.

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