Developing Innovative and Novel Treatment Strategies

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Although we are the experts in treating mental illness, even in the best hands, many of our patients continue to suffer with long-term distressing and disabling symptoms. As we have observed countless times, these ongoing symptoms frequently wreak havoc with our patients' lives by interfering with their work, destroying their relationships, and eroding their capacity to care for themselves. Suicide rates have been climbing, and the numbers are shocking. In 2017, it is estimated that in the United States, there were 1.4 million suicide attempts, with an average of 129 completed suicides per day, for a total of 47,173 suicides for the year (1). Our current therapeutic armamentarium may appear to be impressive with many medication choices, neuromodulation methods, and psychotherapeutic strategies, but the fact is, these approaches are not good enough. We are in desperate need of additional treatments that are effective for our patients with refractory illnesses. It goes without saying that for our patients and their families, the consequences of ineffectively treating severe mental illness are devastating. What may be less obvious is the toll that caring for these patients can take on us as their mental health care providers. Even for the most seasoned clinicians, working with patients who continue to deeply suffer—or worse, complete suicide—can be draining, disheartening, and very demoralizing.

To make progress, we need to have a clearer understanding of the pathophysiological processes that underlie the illnesses we treat as well as how our current treatments work. Despite theories and accumulating data, it may be a surprise to some that we actually do not understand the therapeutic mechanisms of action underlying most of our current treatments. Although the pharmacological actions of our medication treatments have been systematically characterized, to be clear, this is not the same as understanding the mechanism(s) underlying their efficacy in reducing symptoms. As an example, consider the selective serotonin reuptake inhibitors (SSRIs), which are effective antidepressant and antianxiety agents well known to increase the synaptic availability of serotonin by blocking the actions of a protein involved in serotonin reuptake. However, the mechanism of action of SSRIs is not as simple as increasing levels of serotonin. Increases in brain levels of serotonin appear rapidly after taking an SSRI, yet we know that it can take weeks to observe significant reductions in anxiety and depressive symptoms. What are the critical steps between the increase in serotonin levels and the neurochemical and molecular events that lead to response? And where in the brain—that is, in which neural circuits—is it critical for these effects to take place? Another example is electroconvulsive therapy (ECT). Although ECT is one of the most effective treatments for depression, we have little insight into how the induction of seizure activity by the use of electricity can result in the dramatic recovery of our very ill patients.

The news is not all bad. Recently, we have had successes in the development of new treatments in which we also have insights into their novel mechanisms of action. The approval of intranasal esketamine for treatment-resistant depression and of intravenous brexanolone for postpartum depression are two important examples. A considerable number of preclinical studies have been performed that strongly suggest that ketamine's mechanism of action is via blockade of *N*-methyl-D-aspartate receptors, with subsequent changes in critical neuroplasticity growth factors (2, 3). In addition, a recent clinical research study supports the involvement of opiate mechanisms in mediating ketamine's rapid antidepressant effects (4). In the June 2019 issue of the *Journal* (5), the story of the development of brexanolone is nicely presented by National Institute of Mental Health Director Joshua Gordon as an example of successfully translating basic science studies to the development of a novel treatment. Initially, key discoveries were from preclinical studies demonstrating that progesterone metabolites (i.e., the neurosteroid allopregnanolone) have GABA-enhancing and antianxiety-like effects. Clinical research studies followed that provided evidence of a decrease in progesterone and neurosteroids occurring during the postpartum period, and researchers hypothesized that hormonal change was a critical event in vulnerable individuals. This work established a neuroscientific rationale for the subsequent clinical trials that successfully demonstrated the efficacy of the intravenously administered allopregnanolone formulation, brexanolone, for the treatment of postpartum depression.

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This issue of the *Journal* is focused on new findings that exemplify the importance of rigorous clinical research efforts in providing data as a foundation to 1) use our current modalities in novel ways to treat patients, 2) modify and improve

our current treatment methods, and 3) develop completely novel treatment approaches.

Two studies in this issue explore very novel treatment approaches aimed at substance use disorders: cannabidiol (CBD) to treat craving in relation to heroin use disorder, and ketamine in conjunction with a mindfulness-based behavioral modification to treat cocaine dependence. Using a double-blind placebo-controlled design, Hurd et al. (6) tested the effects of the nonintoxicating cannabinoid CBD on cue-induced craving in abstinent individuals with heroin use disorder. Remarkably, their data show that CBD administered over 3 days resulted in a reduction in cue-induced craving and some of its physiological concomitants and that these effects lasted for a week. It is important to underscore that CBD administration also appeared to be safe and well tolerated. In an insightful editorial (7), Dr. David Epstein from the National Institute on Drug Abuse discusses the importance of this finding, its potential limitations, and how these experimentally derived CBD effects may inform future treatment approaches.

The article by Dakwar et al. (8) also provides potentially exciting data relevant to treating substance abuse. These researchers analyzed the effects of a single ketamine infusion relative to an active comparator, midazolam, on outcomes in cocaine-dependent patients. What is most interesting about this study is that the ketamine and midazolam infusions were performed at the beginning of a behavioral intervention, 5 weeks of mindfulness-based relapse prevention (MBRP) training. The results suggest, but do not prove, a synergistic effect of a single ketamine infusion combined with MBRP. Patients receiving this combination had greater positive outcomes, such as reductions in craving and lower likelihood of relapse. However, there was not a group in this study that received the infusions alone in the absence of the MBRP intervention. In her editorial, Dr. Kathleen Brady (9), from the Medical University of South Carolina and a deputy editor of the *Journal*, discusses these findings from the standpoint of their potential as well as in relation to the use of ketamine in populations with substance use disorders.

New applications and modifications of standard transcranial magnetic stimulation (TMS) methodologies are explored in two articles published in this issue. These original research reports are accompanied by a review on the use of TMS written by Dr. Mark George, a professor at the Medical University of South Carolina and a pioneer in the use of TMS to treat psychiatric illnesses. In his review, Dr. George provides a historical and personal account of his involvement with the development of TMS treatment for depression as well as his views on future developments using neuromodulation for treating neuropsychiatric illnesses (10).

In the article by Carmi et al., the effects of high-frequency deep transcranial magnetic stimulation (dTMS) for the treatment of obsessive-compulsive disorder (OCD) were studied (11). This multisite investigation was performed in patients who remained ill after previous treatments and compared 20 Hz dTMS with sham treatment. While other studies have supported the efficacy of TMS in reducing OCD symptoms, the present study used high-frequency stimulation in conjunction with a coil that results in deeper and broader stimulation of the brain designed to target the medial prefrontal and anterior cingulate cortices. These regions were targeted because they are thought to make up a critical component of the hypothesized cortical-striatal-thalamic-cortical loop proposed to be aberrantly functioning in OCD. A unique feature of this study is that the dTMS was applied after a brief period of symptom provocation. Patients received daily dTMS or sham treatments for a total of 29 treatments over 6 weeks. Results demonstrated significant superiority of dTMS compared with sham treatment and, importantly, that high-frequency dTMS appeared to be safe. This clinical trial supports the further exploration of high-frequency dTMS targeted at the medial prefrontal and anterior cingulate in patients with treatment-resistant OCD, and it highlights the possible added benefit of pairing a psychological intervention with neuromodulation.

In another sham-controlled study authored by Philip et al. (12), the efficacy of intermittent theta-burst stimulation (iTBS) targeted at the right dorsolateral prefrontal cortex applied over a 10-day initial treatment period was assessed in veterans with posttraumatic stress disorder (PTSD). Following the blinded phase of the study, all patients received an additional 10 unblinded iTBS treatment sessions. iTBS is a novel approach that uses high-frequency stimulation (50 Hz) that can be delivered much more rapidly and for a shorter period than traditional TMS methods. Although the Food and Drug Administration cleared an iTBS protocol for the treatment of depression, this is the first controlled study of iTBS for the treatment of PTSD. In addition to the obvious advantage of being able to markedly decrease the within-session time and overall length of a course of treatment, this study demonstrated rapid improvement in social and occupational functioning in as early as 2 weeks. Interestingly, in a subset of the patients, the authors were able to use baseline resting-state functional MRI data to predict treatment outcomes. Drs. William McDonald and Sanne van Rooij from Emory University contribute an editorial on this article that provides a more in-depth discussion of the value of iTBS and places the findings from this study in the context of other TMS studies (13).

Deep brain stimulation is another neuromodulation strategy, albeit requiring invasive neurosurgery, that is being used in our most seriously ill patients. In this issue of the *Journal*, Crowell and coworkers (14) report on the long-term outcomes of subcallosal cingulate deep brain stimulation (DBS) in patients with severe and refractory depression. Although results from an earlier sham-controlled trial did not demonstrate superior efficacy (15), results from open-label studies have generally been positive. In the present open-label study, data are presented from DBS patients followed 2–8 years postimplantation. The findings demonstrate that the initial positive effects of DBS appear to be maintained over time in this seriously ill patient group, such that 75% of the

patients maintained their response for more than half of the follow-up period, and 21% demonstrated a continuous response. Considering all of the caveats of an open-label study, these findings are largely reassuring in that the positive outcomes of this invasive procedure appear to be maintained over a prolonged period.

In another study of patients with depression, McCall and colleagues (16) report on the results of a randomized trial in which they assessed the effects of treating insomnia on suicidal ideation. In this double-blind study, controlled-release zolpidem was compared with placebo in patients who were receiving an SSRI. While no significant effect of zolpidem on suicidal ideation was found using the Scale for Suicide Ideation, a positive effect was observed with the Columbia–Suicide Severity Rating Scale and appeared to be the most robust in depressed patients with more severe insomnia. In his thoughtful editorial (17), Dr. Dan Buysse, a sleep expert at the University of Pittsburgh, discusses the rationale for targeting sleep in relation to suicidal ideation, the pros and cons of using zolpidem, and the importance of conducting additional research examining the effects of other sleep-promoting agents on suicidal ideation in depression, as well as in other psychiatric illnesses.

This issue of the *Journal* presents data pointing to new avenues of treatment for our patients. The articles are outstanding examples of the efforts and dedication of researchers who are committed to helping clinicians successfully treat patients whose symptoms are not responsive to treatment. While it takes a long time to accumulate the necessary data to confidently bring new treatment strategies to the clinic, the ideas and early data presented here should provide renewed optimism for clinicians and should engender further support for our clinical and basic science research efforts. It is important to underscore that new treatment development has the greatest likelihood of successfully progressing as we develop a clearer understanding of the neural circuit and cell-specific molecular alterations that mediate the pathophysiological processes underlying mental illnesses. This must also be accompanied by a deeper understanding of how our current treatments work, as well as why, in some individuals, they do not work at all. Such an understanding has the potential not only to lead to new treatments but will also provide a rationale for modifying, and thereby improving, current treatment methods and therapeutic strategies.

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