New Therapeutic Approaches Involving Psychopharmacology, Digital Technology, and fMRI Neurofeedback

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This issue of the *Journal* brings together very clinically relevant papers that present new data aimed at improving interventions for the treatment of alcohol use disorder, binge-eating disorder, psychotic disorders, ADHD, and depression. The issue begins with a timely overview that provides an up-to-date summary on the use of technology in psychiatry (1). Authored by Dr. Phillip Harvey from the University of Miami along with others from the APA Council on Research, this overview summarizes current technological approaches aimed at improving diagnoses, monitoring symptoms, enhancing medication adherence, and facilitating treatment outcomes. The overview also addresses concerns related to the future use of technology in clinical practice, such as the ideal evidence base needed to support the use of specific interventions, as well as FDA regulatory issues involving the approval of new therapeutic applications involving technology. This issue also includes a clinical case conference authored by Drs. Gregory Barber, Charles Nemeroff, and Steven Siegel that presents the evaluation and treatment of a patient with a severe negative reaction to the recreational use of psilocybin (2). In addition to reviewing the clinical management of this challenging case, the authors consider the risks that accompany unsupervised psychedelic use. They also discuss current research examining the therapeutic potential of psychedelics for psychiatric disorders and the relative safety of these efforts. Finally, the authors express concerns related to the more widespread use of these potent agents for "therapeutic" purposes in settings that are not designed to buffer the potential risks.

Two articles in this issue address treatment questions relevant to disorders that involve the neural circuitry underlying reward-related process and addiction. The first examines the efficacy of targeted oral naltrexone treatment for alcohol use disorder in sexual and gender minority men, an understudied population that is at significant risk for negative outcomes related to alcohol binge drinking. The second addresses treatment issues for individuals with binge-eating disorder and obesity by determining the relative efficacies of weight loss therapy, bupropion plus naltrexone, and the combination of these pharmacological and behavioral approaches.

Additional articles in the issue present research that 1) characterizes the efficacy of antipsychotic medications in reducing functional disabilities after a first psychotic episode, 2) assesses the value of the addition of a brief automated cognitive intervention to a ketamine infusion in the treatment of depression, and 3) evaluates the efficacy of fMRI neurofeedback focused on the right inferior frontal cortex in treating ADHD.

Efficacy of Naltrexone for Alcohol Use Disorder in Sexual and Gender Minority Men

Santos et al. (3) report the results of a double-blind placebo-controlled trial assessing the effects of targeted oral naltrexone, 50 mg, versus placebo on binge drinking and other addiction-related outcomes in 120 sexual and gender minority men with moderate symptoms of alcohol misuse. To meet entry criteria, participants could not have more than two alcohol dependence symptoms as assessed with the DSM-IV SCID (they currently would meet mild to moderate alcohol use disorder criteria per DSM-5). The study focused on sexual and gender minority men because they represent a vulnerable and understudied group. Binge drinking was chosen as an outcome measure as in addition to its general deleterious effects, in this population binge drinking, via its effects on risk taking, can be associated with an increased likelihood of acquiring HIV. Participants were male subjects who over the preceding 3 months reported at least one binge drinking episode per week and over that time reported engaging in sexual activity with other men that was accompanied by drinking alcohol. A "targeted" dosing strategy, coupled with 12 weekly sessions of medication management training, was used such that participants were expected to take their medication when anticipating the possibility of episodes of heavy drinking and

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during periods of alcohol craving. The data revealed significant effects of naltrexone on reducing primary outcome measures associated with binge drinking. More specifically, findings from the intention-to-treat analyses found that the targeted use of naltrexone resulted in significantly less drinks in the past 30 days and reductions in any binge drinking during the past week and the number of drinking days in the past week. As a secondary measure, subjective ratings of alcohol craving were also found to be significantly decreased in the naltrexone group. Despite the effects of naltrexone on alcohol consumption, the naltrexone group did not differ from placebo in the prevalence of reported risk-related sexual behaviors. It is important to note that at the 6-month follow-up assessment, individuals who received naltrexone, compared with those treated with placebo, continued to report significant decreases in binge drinking. Overall, the findings from this study are not surprising as they are consistent with the established efficacy of naltrexone for the treatment of alcohol use disorder. However, the importance of the study lies in the demonstration that targeted naltrexone treatment is effective in this understudied population of sexual and gender minority men. In an editorial (4), Dr. Jonathan Avery from Weill Cornell Medicine emphasizes that alcohol use disorder is generally undertreated, and after discussing the implications of the findings from this study advises that naltrexone should be more frequently prescribed by psychiatrists in their treatment of individuals struggling with alcohol misuse.

Naltrexone Plus Bupropion and Behavior Weight Loss Therapy in Treating Binge-Eating Disorder Patients with Comorbid Obesity

Among the eating disorders, binge-eating disorder is thought to be the most common, estimated to have a 3.5% lifetime prevalence in women and a 2.0% lifetime prevalence in men (5). While it was not considered as a formal diagnosis in DSM-IV, DSM-5 sets forth criteria for binge-eating disorder that include recurrent episodes of binge eating over at least a 3-month period that are associated with rapid food consumption, continuing to eat while feeling full, and eating when not hungry. Additionally, these eating symptoms are accompanied by feelings of embarrassment, disgust, and guilt. Binge-eating disorder frequently co-occurs with obesity but, as Grilo et al. point out, differs behaviorally and likely pathophysiologically from general obesity (6). Current effective treatments for binge-eating disorder include cognitive behavioral therapy and lisdexamfetamine, which is approved by the FDA for this indication. Additional treatments are needed, and Grilo et al. present efficacy data from a double-blind placebo-controlled randomized clinical trial in patients with binge-eating disorder and comorbid obesity that compares the efficacy of 16 weeks of treatment with four interventions: weekly sessions of behavioral weight loss therapy plus placebo (N=35), bupropion/naltrexone (N=32), bupropion/naltrexone with weekly sessions of behavioral weight loss therapy (N=35), and placebo (N=34). Treatment with bupropion/naltrexone began at low doses and was increased as tolerated to a total dose at 4 weeks of sustained-release naltrexone, 32 mg/day, and sustained-release bupropion, 360 mg/day. These treatments were selected because bupropion/naltrexone is currently FDA approved for weight loss in obese adults, naltrexone is approved for treating opioid and alcohol use disorder, and bupropion is approved for treating depression and smoking cessation. Additionally, earlier studies suggest that behavioral weight loss therapy is effective for reducing binge eating and promoting weight loss. Behavioral weight loss therapy involves focusing on healthy eating behaviors and promoting physical activity along with other behavioral and cognitive techniques. Results from an intention-to-treat analysis demonstrated a significant main effect of behavioral weight loss therapy and a significant effect of medication but not a significant interaction. Specifically, the binge eating remission rates were 17.7% for placebo, 31.3% for naltrexone/bupropion, 37.1% for behavioral weight loss plus placebo, and 57.1% for naltrexone/bupropion plus weight loss therapy. When assessing the frequency of binge eating during the previous month, behavioral weight loss therapy resulted in significantly less binging at all time points when compared with placebo, whereas the naltrexone/bupropion treatment significantly decreased binging only at the 1- and 2-month assessment periods. The behavioral weight loss intervention also resulted in significant weight reductions beginning at 2 months of treatment. In contrast, naltrexone/bupropion treatment did not result in significant weight loss. Again, for weight loss, no significant interactions between naltrexone/bupropion and weight loss therapy were detected. Also, weight loss therapy was generally associated with significant reductions in eating disorder-related psychopathology including depression scores and metabolic parameters such as cholesterol and Hb1Ac; this was not the case for medication therapy. Overall, the results from this study point to both naltrexone/bupropion and behavioral weight loss therapy as being effective for decreasing symptoms associated with binge-eating disorder and suggest that behavioral weight loss therapy is further effective for weight reduction in individuals with binge-eating disorder and obesity.

Antipsychotics Reduce Work-Related Disability Associated With First Psychotic Episodes

There is no question that antipsychotic medications are effective in reducing psychotic symptoms. However, the longer-term impact of these medications on functional outcomes has not been as well documented. This matter is addressed by the study of Solmi et al. (7), where follow-up data from a large cohort of Swedish individuals after their first nonaffective psychotic episode (N=21,551) was used to link work-related disability (sickness absence and disability pension) to antipsychotic use. Longitudinal data from these individuals with schizophrenia spectrum disorders was

collected over a maximum of 11 years, with the median time of follow up being 4.8 years. Of the 21,551 individuals with first-episode nonaffective psychoses, 13,392 received antipsychotics, and over the follow-up period 77% of these individuals had a median of three antipsychotic treatment gaps. Of the individuals who received antipsychotics, 7,685 also had a medically certified sickness absence or a disability pension. When these individuals took their antipsychotic medication, their risk of this disability was decreased by 35%. Also, the use of antipsychotics significantly decreased the likelihood of longer-term (greater than 90 days) disabilities by 45%. Overall, significantly better functional outcomes were associated with the use of long-acting injectable formulations. While not unexpected, these findings document that within vulnerable individuals, continuous antipsychotic treatment has long-term benefits on reducing real world disabilities.

Lack of Efficacy of fMRI Neurofeedback in ADHD Children

Functional MRI neurofeedback is receiving considerable attention as a potential novel intervention with the capacity to promote neuroplasticity by teaching individuals to self-regulate the function of specific brain regions or networks. Lam and colleagues (8) explore the use of fMRI neurofeedback aimed to help participants learn to modulate right inferior frontal cortex function as a potential treatment for boys with ADHD. The right inferior frontal cortex was selected as a target because alterations in the function of this region have been linked to ADHD as the right inferior frontal cortex is involved in attention and cognitive control. Also, an earlier non-placebo-controlled fMRI neurofeedback study showed this region to be a promising ADHD treatment target (9). The current double-blind placebo-controlled trial involved MRI scanning sessions over a 2-week period in which the active group was trained in a "self-regulation" paradigm such that they learned to regulate activation of the right inferior frontal cortex. In the active treatment group, during training, an individual's capacity to increase and decrease activation of the right inferior frontal cortex was reflected by similar changes in a rocket viewed on a video screen. The comparator group received sham neurofeedback. Follow-up assessments were 1 week and 6 months after completion of the training. Forty-four boys with ADHD constituted each group. Participants could be receiving ADHD medication if the dose was stable for a minimum of 2 weeks, but stimulants were withheld 24 hours before the fMRI training sessions. Unfortunately, the results demonstrated no advantage of neurofeedback. Both the active and sham groups exhibited a reduction in the primary outcome measure when comparing parent-rated ADHD rating scale scores at baseline with those at the end of treatment. Also, ADHD ratings increased in both groups when assessed at the 6-month follow-up. The secondary outcome measures, other symptoms, and performance on a go/no go task also did not show an advantage for the active treatment group when assessed at 6 months. It is surprising that compared with the active treatment group, the sham treatment group exhibited decreased irritability and improved motor inhibition assessed with the go/no go task. Analyses of the imaging data revealed increased activation in the right inferior frontal cortex and other brain regions involved in self-regulation in the active compared to the sham group. However, individual differences in right inferior frontal cortical activation were not significantly correlated with symptom changes associated with the interventions. In his editorial, Dr. James McGough from UCLA (10) discusses the history of the use of various types of neurofeedback for ADHD treatment in relation to the current findings that demonstrate a lack of superiority of fMRI neurofeedback compared with sham feedback. He calls into question whether further work with neurofeedback methods for ADHD treatment should be pursued and emphasizes the lack of convincing evidence to support current clinical use.

Ketamine Combined With Automated Self-Association Training Prolongs Ketamine's Antidepressant Effects

Ketamine infusions are effective for the acute reduction of depressive symptoms, but the efficacy of a ketamine infusion is short lived. How to maintain the acute ketamine response, and how to optimally treat patients after ketamine administration, have become important clinical questions. In this regard, the repeated administration of ketamine is a strategy that is commonly used to maintain and prolong treatment responses, although the specific parameters related to the frequency of ketamine administration and the length of treatment with ketamine need to be further established. Furthermore, the potential negative consequences of repeated ketamine administration are not clear. While at the molecular level ketamine has numerous effects, its impacts on the NMDA receptor system have been hypothesized to promote neuroplasticity and therefore could hypothetically facilitate the efficacy of other behavioral and/or cognitive interventions. Relevant to this premise, Price and colleagues (11) explore the possibility that one ketamine infusion can interact with a course of automated self-association training (ASAT) to facilitate longer treatment responses in individuals with treatment-resistant unipolar depression. ASAT is a computerized training program that uses positive conditioning methods with the goal of enhancing implicit positive self-associations in depressed patients. Data from this double-blind clinical trial compared outcomes (primary outcome measure: Montgomery-Åsberg Depression Rating Scale) among three groups of depressed participants who were maintained on their ongoing antidepressant medications during the study: ketamine/ASAT (N=53), ketamine/sham ASAT (N=50), and saline/ASAT (N=51). Participants received an infusion of either saline or ketamine (0.5 mg/kg) and 1 day later began the automated cognitive intervention, receiving approximately 20 minutes of ASAT or sham ASAT two times a day over the following 4 days. Assessments

were performed until the study ended at 30 days. Results demonstrated that ketamine, compared with saline administration, resulted in significant reductions in depressive symptoms 24 hours postinfusion. In the individuals receiving ketamine/ASAT, the acute reduction in symptoms was maintained over the 30-day assessment period. The ketamine/sham ASAT individuals showed an initial ketamine-induced decrease in symptoms, which, over time, was followed by an increase in symptoms, while the saline/ASAT group had less of an initial decrease in symptoms and remained at this somewhat improved level over the 30-day assessment period. These results are potentially exciting as they point to a synergy between ketamine and ASAT and a treatment paradigm to prevent relapse in ketamine-treated patients. The extent to which the interaction between ketamine and ASAT is mediated by ketamine-induced neuroplasticity cannot be determined from this study, but it is important to note that the ASAT treatment was also found to maintain the modest effects of the "inactive" saline infusion. In an editorial, Dr. Alan Schatzberg from Stanford University (12) addresses issues related to the long-term maintenance of initial ketamine responses, the relatively small effects observed in the current study, and the likely utility of optimizing combined approaches, pairing acute ketamine treatment with other behavioral and psychotherapeutic interventions.

Conclusion

This issue of the *Journal* presents new findings that are directly relevant to patient care. The use of technological advances in psychiatry are brought up to date with the latest developments that facilitate the real-time and real-world monitoring of symptoms and functional outcomes, as well as technologies such as virtual reality that can be used for treatment. Other insights from the articles in this issue include 1) how targeted naltrexone treatment effectively reduces binge drinking in sexual and gender minority men; 2) that both naltrexone plus bupropion and behavior weight loss therapy can reduce symptoms in binge-eating disorder patients with comorbid obesity, but in these patients behavioral weight loss therapy appears to be more effective than the medication regimen for weight reduction; 3) how within schizophrenia spectrum disorder individuals, adherence to antipsychotic medication treatment after a first psychotic episode is linked to improvements in real-world functional disabilities; 4) how despite its influences on brain function, fMRI neurofeedback focused on the right inferior frontal cortex is not effective in the treatment of ADHD; and 5) evidence supporting a synergistic effect between one ketamine infusion and automated self-association training for maintaining ketamine-induced antidepressant responses in patients with treatment-resistant depression.

Some advances in clinical care appear to be incremental, while others have the potential to be transformative. Both types of advances are represented in the articles in this issue, and both are important. For example, demonstrating that targeted naltrexone treatment is effective for binge drinking is by itself not new, but clear evidence that it works in an understudied minoritized population is important and has immediate clinical utility. Similarly, the data presented regarding the use of naltrexone plus bupropion and weight loss therapy for obese individuals with binge-eating disorder provides clinicians with data to support decision making when considering treatment options for these patients. The finding demonstrating that a cognitive/behavioral intervention can prolong the antidepressant effects of one ketamine infusion provides a potential solution to the short-term effects of ketamine and, while not clear from this study, could be related to ketamine's proposed neuroplasticity effects. Last, the use of new technologies to collect real-time ecologically relevant patient data and to provide automated customized interventions has the potential to be transformative, as do methods using real-time, personalized neural circuit-based biofeedback treatment approaches. These new therapeutic approaches are considerably further away from the clinic and will require significant additional investigation and development. To have the most impact on improving the lives of our suffering patients it is critical that we engage in research efforts across clinical, translational, and basic neuroscience domains. Efforts should be focused both on studies that are immediately clinically relevant, building on our knowledge of current effective treatments, as well as on exploring highly novel and sometimes riskier strategies that are based on preclinical neuroscience discoveries.

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Disclosures of Editors' financial relationships appear in the April 2022 issue of the *Journal*.

Am J Psychiatry 2022; 179:881–885; doi: 10.1176/appi.ajp.20220866

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