# Insights Into Improving Clinical Outcomes Across Psychiatric Disorders and Medical Comorbidities

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This issue of the *Journal* brings together a variety of papers that address clinically relevant treatment issues. In addition to original research papers, we include a commentary by Salvi et al. (1) that presents an argument for using principles of dynamical systems theory to guide future work characterizing and understanding psychopathology. This approach, which uses mathematical modeling, is facilitated by assessing behavior and cognition with fine-grained temporal analyses, akin to approaches used in quantitating physiological measures. We also include two reviews in this issue with public health implications, one that highlights important gaps in treating comorbid medical and psychiatric disorders, the other discussing the treatment of patients with opioid use disorder. The first review addresses disparities in the treatment of cardiovascular disorders in psychiatric patients. By performing a large meta-analysis, Solmi et al. (2) show that patients with psychiatric illnesses receive lower rates of screening and treatment for cardiovascular disorders, and, not surprisingly, this is most prominent in patients with schizophrenia. This disparity in care adds to the literature documenting the negative consequences of suffering from a psychiatric illness in relation to medical outcomes. The finding also supports poorly treated cardiovascular disease as a contributor to the reduced longevity that occurs in some psychiatric patients, especially those suffering from severe disorders. The second review, by McCarty and colleagues (3), presents evidence supporting the efficacy of office-based methadone treatment for patients with opioid use disorder who are already on a stable methadone treatment regimen. Current federal regulations limit methadone treatment to federally certified opioid treatment programs, which for many individuals are difficult to access. Based on their survey of the data, the authors argue for changes in federal regulations that would enable the more widespread use of methadone treatment in outpatient settings. Such a change would increase access and reduce disparities in opioid use disorder treatment that are related to social inequities and a lack of available treatment centers in underresourced communities.

### Testing the Efficacy of Combining Varenicline and Naltrexone for Treating Heavy-Drinking Smokers

Ray et al. (4) report findings from a double-blind randomized clinical trial (N=165) comparing the combination of varenicline and naltrexone with varenicline plus placebo for the treatment of smoking and alcohol use in heavy drinkers. The authors point out the need for interventions that target both smoking and drinking, since they commonly co-occur in individuals with alcohol use disorder. Varenicline, FDA approved for smoking cessation therapy, is a partial agonist of the α4β2 nicotinic acetylcholine receptor subtype; naltrexone, FDA approved for alcohol use disorder, is an antagonist of the μ-opioid receptor with weaker effects at the κ-opioid receptor and even weaker effects at the δ-opioid receptor. In this study, the active treatment phase duration was 12 weeks, during which participants received varenicline, 2 mg/day, with either naltrexone, 50 mg/day, or placebo. After treatment, patients were followed for an additional 14 weeks, and over this period 72% completed the study. When assessed at the end of the study, across both treatment groups the smoking quit rate was 35.8%. However, and unexpectedly, individuals in the varenicline/placebo group did significantly better than those in the varenicline/naltrexone group, with smoking quit rates of 45.1%, and 26.5%, respectively. In relation to alcohol use, both treatments were associated with reduced daily alcohol intake. While there was a trend in the data that suggested that the combination of varenicline and naltrexone was superior to varenicline plus placebo, this finding did not reach statistical significance. Although further studies should be done, these data suggest that varenicline alone may be the best treatment for heavy drinkers who also smoke even though naltrexone is FDA approved for the treatment of alcohol use disorder. Dr. Andrea King from the University of Chicago and Dr. Lisa Fucito from Yale University discuss in their editorial (5) how smoking and alcohol use can interact to interfere with recovery and consider more general issues relevant to using combination medication therapies in individuals with substance use disorders.

**This issue of the *Journal* provide[s] new knowledge and perspectives focused on improving treatment outcomes for various disorders, including opioid use disorder, alcohol use disorder, ADHD, anorexia nervosa, schizophrenia, and cardiovascular disease comorbid with psychiatric disorders.**

### Gabapentin's Effects on GABA and Glutamate Levels in Relation to Treatment Efficacy in Alcohol Use Disorder

Prisciandaro and colleagues (6) report on magnetic resonance spectroscopy (MRS) findings acquired from patients with alcohol use disorder during their participation in a clinical trial assessing the efficacy of gabapentin. Gabapentin binds to the $\alpha_2\delta$ calcium channel subunit, which results in various intracellular and neurotransmission-related effects, and it also activates KCNQ3/5 voltage-gated potassium channels. The behavioral findings from a previously published clinical trial demonstrated that 16 weeks of gabapentin treatment (up to 1200 mg/day) resulted in more individuals with less heavy drinking days and more total abstinence when compared with placebo (7). Interestingly, this effect of gabapentin was only significant in the participants who had high levels of alcohol withdrawal prior to the study and was not apparent in individuals with low levels of alcohol withdrawal. During the study, 68 of the participants (37 in the gabapentin treatment group and 31 in the placebo group) underwent MRS imaging prior to and 2 weeks after the initiation of treatment to assess dorsal anterior cingulate cortex GABA and glutamate levels. Consistent with ideas about how gabapentin affects neurotransmission, the authors found that 2 weeks of gabapentin treatment resulted in a reduction in glutamate and an increase in GABA levels. However, the effects of gabapentin on these neurotransmitters depended on the levels of abstinence achieved by the participants during the first 2 weeks of treatment. Specifically, individuals with fewer abstinent days between scans (40%−50% days abstinent) had increases in glutamate and decreases in GABA, whereas the opposite, decreased glutamate and increased GABA, was observed in individuals with more abstinent days (85%−95%) between scans. Importantly, and with potential clinical relevance, gabapentin-treated individuals with greater increases in dorsal anterior cingulate cortex glutamate levels during the first 2 weeks of treatment had more days abstinent throughout the study. While complicated and requiring further study, these findings support the idea that the therapeutic efficacy of gabapentin in the treatment of alcohol use disorder involves the modulation of GABA and glutamate transmission in regions of the frontal cortex that are involved in cognitive control and in the processing of negative affect and pain (8).

### Anticholinergics and Cognitive Impairment in the Treatment of Schizophrenia

Many antipsychotic medications, as well as other psychotropic medications, have anticholinergic effects, and anticholinergic medications are commonly used to treat antipsychotic-induced extrapyramidal symptoms such as dystonia, akathisia, and pseudoparkinsonism. Despite their potential benefit, anticholinergics can have a negative impact on cognition, which is already impaired in patients with schizophrenia. To characterize the impact of anticholinergic medication treatment on cognitive function in patients suffering from schizophrenia or schizoaffective disorder, Joshi et al. (9) performed an analysis of data from a large group of patients (N=1,120) from the Consortium on the Genetics of Schizophrenia−2 cohort. Using an established method, the authors calculated an anticholinergic burden score for each study participant and related these scores to individual scores of cognitive function assessed with the Penn Computerized Neurocognitive Battery. The findings demonstrated that individual differences in anticholinergic burden were negatively associated with cognitive performance, which was present across all cognitive domains that were assessed (i.e., abstraction and mental flexibility, attention, working memory, face memory, verbal memory, spatial memory, spatial ability, and emotion processing). Importantly, the association between anticholinergic burden and cognitive impairment could not be accounted for by other illness-related factors such as the use of first- versus second-generation antipsychotics, severity of positive and negative symptoms, or illness duration. The authors point out that the average anticholinergic burden for schizophrenia patients is relatively high and in the range of that found to be associated with an increased risk of developing dementia when assessed in other populations (10). As a recommendation, the authors encourage clinicians to be mindful of their patients' anticholinergic burden as they work to optimize pharmacotherapy in these chronically and severely ill patients.

### Relapse After Acute Treatment for Anorexia Nervosa

Anorexia nervosa is a chronic illness with significant morbidity and mortality. To better understand the course of the illness after acute treatment, and to help define criteria for remission, Walsh et al. (11) performed secondary analyses on data from a previous clinical trial (12). In the original clinical trial, the authors compared the efficacy of 1 year of treatment with fluoxetine to placebo in patients with anorexia nervosa who were previously acutely treated for weight restoration. During this 1-year study, all patients also received concomitant cognitive behavioral therapy. Results from the initial study, published in 2006, found no significant differences in time to relapse between the fluoxetine- and placebo-treated groups. In the secondary analysis published in this issue, Walsh and colleagues were interested in further characterizing the time course to relapse as well as examining whether they could find an inflection point in the relapse curve that would provide data for a more objective definition of remission. Ninety-three women with anorexia nervosa entered the study, of whom only 40 completed it. The risk of relapse increased after the beginning of the study and peaked at 60 days. After 60 days, the risk of relapse gradually declined, but there was no evidence of a dramatic inflection point in the relapse time course curves. The findings underscore the continuing risk of relapse among patients with anorexia nervosa after acute treatment for weight restoration, even those receiving medications and psychotherapy. Dr. Cynthia Bulik from the University of North Carolina at Chapel Hill discusses in her

editorial (13) the overall findings in relation to the lack of significant progress that has been made in developing new and improved treatments for anorexia nervosa. She emphasizes the importance of the findings documenting increasing rates of relapse up to 60 days after weight restoration as evidence to support the need for appropriate resources and funding to provide the ongoing interventions needed for individuals suffering from anorexia nervosa.

### Factors Associated With Stimulant Treatment Outcomes in Patients With ADHD

Stimulants have long been established as highly effective treatments for ADHD, and Brikell et al. (14) use prescription data from a large cohort of individuals with ADHD (N=9,133) from the Danish iPSYCH2012 sample to characterize genetic and nongenetic factors that are related to treatment outcomes with stimulants. Understanding the factors that are associated with stimulant adherence and discontinuation is particularly relevant for facilitating successful long-term outcomes in ADHD patients. Within this group of ADHD patients, the average age at ADHD diagnosis was 12 years, and 81% were treated with stimulants within 2 years of diagnosis. Forty-five percent of the stimulant-treated patients discontinued their stimulants within 2 years of starting treatment, and 15% switched to a nonstimulant medication. Regarding genetics, it is interesting that the polygenic risk score (PRS) for ADHD was not related to any aspects of the treatment. However, the PRSs for schizophrenia and bipolar disorder were associated with a relatively small, but significant, increased risk of discontinuing stimulant treatment. More prominent effects were observed for comorbid psychiatric conditions: individuals with comorbid OCD, anxiety disorder, bipolar disorder, or substance use disorder were less likely to be treated with stimulants, and discontinuation of stimulant treatment was more likely to occur in patients with comorbid autism spectrum disorder, anxiety disorder, bipolar disorder, or substance use disorder. Switching treatment to a nonstimulant medication was more likely to occur in the presence of comorbid oppositional defiant disorder, tics, anxiety disorder, and substance use disorder. In her editorial (15), Dr. Jonna Kuntsi from King's College London discusses issues relevant to the treatment of ADHD and the genetic, demographic, and clinical findings from this study; Dr. Kuntsi also underscores the potential clinical relevance of the findings implicating psychiatric comorbidities in relation to stimulant treatment outcomes.

### Conclusions

Several of the papers in this issue address pragmatic concerns that, if attended to, could have immediate and direct positive impacts on patient care. These include 1) addressing factors that contribute to the disparities in care for psychiatric patients with cardiovascular disease, 2) promoting changes in health care policy to enable easier and more equitable access to outpatient methadone treatment, 3) developing resources and treatment programs focused on longer-term systematic interventions in patients with anorexia nervosa, and 4) minimizing medication-related anticholinergic burden in schizophrenia patients to decrease medication-associated cognitive impairments.

Other interesting findings of clinical relevance that are presented in this issue are relevant to treating patients with ADHD and alcohol use disorder. In relation to ADHD treatment, the findings point to the importance of accounting for psychiatric comorbidities when treating ADHD patients with stimulants. For alcohol use disorder, data are presented that suggest that treatment with varenicline alone may be a better treatment than varenicline combined with naltrexone for heavy alcohol drinkers who also smoke. Finally, the paper by Prisciandaro et al. (6) highlights the potential importance of personalized medicine approaches, as it demonstrates, in patients with alcohol use disorder, complex interactions between a medication treatment, its effects on neurotransmitter systems, and patient features. In this case, the authors show differential effects of gabapentin on dorsal anterior cingulate cortex GABA and glutamate levels that depend on how abstinent the patient is early in treatment.

Taken together, the papers presented in this issue of the *Journal* provide new knowledge and perspectives focused on improving treatment outcomes for various disorders, including opioid use disorder, alcohol use disorder, ADHD, anorexia nervosa, schizophrenia, and cardiovascular disease comorbid with psychiatric disorders.


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### REFERENCES


1. Salvi JD, Rauch SL, Baker JT: Behavior as physiology: how dynamical systems theory could advance psychiatry. Am J Psychiatry 2021; 178:791–792
2. Solmi M, Fiedorowicz J, Poddighe L, et al: Disparities in screening and treatment of cardiovascular diseases in patients with mental disorders across the world: systematic review and meta-analysis of 47 observational studies. Am J Psychiatry 2021; 178:793–803
3. McCarty D, Bougatsos C, Chan B, et al: Office-based methadone treatment for opioid use disorder and pharmacy dispensing: a scoping review. Am J Psychiatry 2021; 178:804–817
4. Ray LA, Green R, Enders C, et al: Efficacy of combining varenicline and naltrexone for smoking cessation and drinking reduction: a randomized clinical trial. Am J Psychiatry 2021; 178: 818–828
5. King A, Fucito L: Cigarette smoking and heavy alcohol drinking: the challenges and opportunities for combination treatments. Am J Psychiatry 2021; 178:783–785
6. Prisciandaro JJ, Hoffman M, Brown TR, et al: Effects of gabapentin on dorsal anterior cingulate cortex GABA and glutamate levels and

their associations with abstinence in alcohol use disorder: a randomized clinical trial. Am J Psychiatry 2021; 178:829–837
7. Anton RF, Latham P, Voronin K, et al: Efficacy of gabapentin for the treatment of alcohol use disorder in patients with alcohol withdrawal symptoms: a randomized clinical trial. JAMA Intern Med 2020; 180:728–736
8. Shackman AJ, Salomons TV, Slagter HA, et al: The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat Rev Neurosci 2011; 12:154–167
9. Joshi YB, Thomas ML, Braff DL, et al: Anticholinergic medication burden–associated cognitive impairment in schizophrenia. Am J Psychiatry 2021; 178: 838–847
10. Coupland CAC, Hill T, Dening T, et al: Anticholinergic drug exposure and the risk of dementia: a nested case-control study. JAMA Intern Med 2019; 179:1084–1093
11. Walsh BT, Xu T, Wang Y, et al: Time course of relapse following acute treatment for anorexia nervosa. Am J Psychiatry 2021; 178: 848–853
12. Walsh BT, Kaplan AS, Attia E, et al: Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. JAMA 2006; 295:2605–2612
13. Bulik CM: From awareness to action: an urgent call to address the inadequacy of treatment for anorexia nervosa. Am J Psychiatry 2021; 178:786–788
14. Brikell I, Wimberley T, Albiñana C, et al: Genetic, clinical, and sociodemographic factors associated with stimulant treatment outcomes in ADHD. Am J Psychiatry 2021; 178: 854–864
15. Kuntsi J: The conundrum of treatment discontinuation of stimulant medication for ADHD despite its efficacy. Am J Psychiatry 2021; 178:789–790