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How to Best Treat Patients With Schizophrenia and Co-Occurring Alcohol Use Disorder

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Individuals with serious mental illness, including schizophrenia and schizoaffective disorder, have rates of alcohol use disorders greater than those in the general population.[1] The rates are even higher among those in treatment, particularly in high intensity settings, and comorbidity is associated with worse outcomes.[2] Comprehensive psychosocial treatments, which include staged treatments, outreach, and motivational interventions, among others, have been shown to be effective, but there are barriers to implementing these treatments widely.[3] Further, no consensus exists on the optimal pharmacologic management for these individuals. A small literature exists that evaluates the use of medications to treat alcohol use disorder in comorbid samples with some success (eg, naltrexone and acamprosate),[4–6] but these treatments also have not been widely adopted.[7] Since antipsychotics are the mainstay of treatment for schizophrenia and schizoaffective disorder, one important research question with direct clinical relevance is: Are antipsychotics with long-acting injectable formulations better suited for those with alcohol use disorder comorbidity?

In this issue of the *Journal*, Green and colleagues[8] attempt to address this question. The authors report on a 6-month randomized clinical trial comparing long-acting injectable (LAI) risperidone with oral risperidone in 95 individuals with schizophrenia or schizoaffective disorder and alcohol use disorder. The authors hypothesized that the LAI formulation would be superior in decreasing alcohol consumption because (1) LAI formulations compared to oral formulations lead to lower dopamine receptor occupancy, and this will be associated with a decrease in alcohol use; and (2) the LAI formulation will improve adherence to medication and lead to better outcomes. Study outcomes focused on measures of drinking consumption, psychiatric symptoms, and functioning. Results of the trial show that there were no statistical differences in alcohol use outcomes between groups, although the authors found that heavy drinking actually *increased* in the oral group, but not in the LAI group. There were no differences in psychiatric symptoms between groups. The results of other outcomes, such as medication compliance, favor the use of LAI risperidone, suggesting it may be a better medication for those with comorbid alcohol use disorder.

The first hypothesis regarding dopamine receptor occupancy and its role in drinking could not be directly tested in this study, and, in fact, there were no significant differences in alcohol use consumption measures between groups. However, there was an increase in heavy drinking in the oral risperidone group. The authors suggest that this increase in drinking is indirect support for their hypothesis that dopamine D_2 receptor occupancy, presumably higher in the oral group, is associated with higher drinking rates. This hypothesis does fit with at least one version of the self-medication hypothesis—the hypothesis that patients drink to counteract the effects of antipsychotic medications. However, given the lack of a statistical significance between groups, the lower plasma levels of risperidone, and no direct test of receptor occupancy, the results can only be considered suggestive.

The finding that heavy drinking actually *increased* in 1 of the groups is highly unusual for a treatment study of alcohol use disorders, even among those with psychiatric comorbidity. It has been well documented that research subjects usually report a decrease in drinking in clinical trials testing pharmacologic interventions for alcohol use disorders, and, in fact, the placebo effect often undermines the results of clinical trials in alcohol use disorders.[9] This decrease in drinking during clinical trials has also been fairly consistently found in treatment studies with individuals with serious mental illness taking antipsychotic medications.[4,5] It should be noted that those studies mostly tested adjunctive medications for alcohol use disorders and required participants to be stable on their antipsychotic medication prior to randomization. In the present study, participants underwent antipsychotic medication changes as part of the research study. These changes may have contributed to clinical instability, which could lead to an increase in drinking. A significant number of subjects (37.9%) did report an exacerbation of symptoms. However, the authors found no group differences in psychiatric symptoms and no clear relationship between drinking and symptom exacerbation. Nevertheless, the authors do important work by evaluating this potential relationship, and the (lack of) finding may be due, at least in part, to the difficulty in evaluating a link between drinking and symptom worsening given the complexity of the patient population.

The authors did find that, as hypothesized, adherence was better in the LAI group than in the oral group. Adherence is thought to be an important factor in the management of patients with serious mental illness, particularly among

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those with comorbid substance use disorders. It is clinically sound to consider that an intervention that improves adherence is likely to improve other outcomes, including risk of hospitalization. Previous studies have evaluated the potential superiority of LAI risperidone in treating schizophrenia without comorbidity. Several studies have suggested that LAI is indeed superior to other antipsychotic medications in terms of psychiatric outcomes and health care cost.[11,12] LAI medications in general have been associated with lower rates of discontinuation, recurrence of symptoms, and hospitalization and better functioning and quality of life.[12] However, in a large Veterans Affairs study,[13] LAI risperidone was compared to the "physicians' choice" of oral antipsychotic for individuals at high risk of hospitalization. Contrary to the hypothesis, LAI risperidone was not superior for psychiatric outcomes, including the preventing of rehospitalization. Further, side effects and rates of adverse events, particularly injection site adverse events, were higher in the LAI group.

Given the possible side effects associated with LAI formulations, the authors in this study closely monitored side effects.[8] Injection site adverse events were not reported in the LAI group, and there were no significant differences in side effects between groups. It should be noted that a large percentage (79%) of subjects overall reported adverse events, confirming that risperidone, like other medications commonly used to treat schizophrenia, has a high side-effect burden, suggesting the need to develop better pharmacologic strategies.

Several limitations from this study highlight the difficulty in conducting trials in comorbid populations.[8] First of all, recruiting adequate samples to answer the primary question in a study with comorbid populations is always a challenge. In this study, the authors recruited a relatively large sample of 95 subjects, yet, it should be noted that in order to recruit this number, subjects were recruited from 4 different sites. Conducting clinical trials across different sites is both costly and requires good collaboration between investigators. The authors should be commended for their ability to successfully recruit an adequate sample size and conduct this type of study. Second, the presence of psychiatric comorbidities, concomitant treatment with other psychiatric medications, and participation in other forms of behavioral treatments complicate interpretation of a treatment study but are part of the reality of conducting studies in real world clinical populations.

Despite these limitations, this study by Green and colleagues[8] is important for several reasons. The undertaking of well-designed, controlled studies with complicated clinical populations is sorely needed. Given the increasing emphasis on evidence-based practice, clinicians who treat patients with dual diagnoses should not need to follow treatment algorithms based on studies conducted primarily with noncomorbid groups. Further, designing studies that address practical clinical questions is an important endeavor. It has long been hypothesized that LAI formulations of antipsychotic medications are advantageous for individuals with comorbid substance use disorders, but this theory has not previously been formally and rigorously tested. Additionally, as with any important clinical research, interesting follow-up questions present themselves from the results. Is LAI risperidone superior to other antipsychotic medications in this comorbid group of patients? Would medications to treat alcohol use disorder be effective adjunctive medications to LAI risperidone? This question is particularly interesting in terms of naltrexone, since it, too, has a long-acting injectable formulation; and if LAI therapy has an advantage in terms of adherence, it may be particularly useful in this patient population. In fact, some pilot work has suggested that this formulation of naltrexone may be effective for this patient population.[4] More clinical studies, like the study conducted by Green and colleagues,[8] will be needed in determining the most effective pharmacologic strategy for this patient population.

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