Treatment of Schizophrenia and Comorbid Substance Abuse: Pharmacologic Approaches

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Co-occurring substance use disorder is common among patients with schizophrenia, and its presence greatly worsens the course of schizophrenia. A number of theories have been introduced to explain the increased rate of substance use disorder in these patients. These theories include the notion that substance use could trigger psychotic symptoms in vulnerable individuals and the idea that the substances are used to self-medicate symptoms of schizophrenia. Our group and others have advanced a neurobiological hypothesis to explain this comorbidity—that a mesocorticolimbic brain reward circuit underlies the substance use disorder in patients with schizophrenia. Treatment of substance use disorder in these patients is best done with integrated treatment programs that combine psychosocial interventions with pharmacotherapy. Recent data suggest that the atypical antipsychotic clozapine and perhaps other atypical agents may lessen substance use in patients with schizophrenia. My colleagues and I have proposed that clozapine's effect in these patients may be related to its ability to decrease the brain reward circuit dysfunction. Research is continuing on the use of atypical antipsychotics in patients with schizophrenia and comorbid substance abuse. The adjunctive use of naltrexone or other agents also may be helpful. Further research on the optimal pharmacologic approach to patients with dual diagnosis is needed. *(J Clin Psychiatry 2006;67[suppl 7]:31–35)*

Schizophrenia is an illness that has an onset in late adolescence or early adulthood, and patients' functioning often begins to decline prior to the first episode. Investigators throughout the world are attempting to find ways to treat patients during the first episode of schizophrenia, or even before, to improve the course of this devastating disorder. Substance use disorder often co-occurs with schizophrenia, including the early phase of the disorder, and is associated with a poor outcome. Therefore, attempts to identify and treat substance use disorder in these patients are essential if the trajectory of schizophrenic illness is to be improved. In this article, the co-occurrence of substance use disorder in patients with schizophrenia is examined, and the potential biological basis of the co-occurring disorder and existing pharmacologic approaches to treating these patients are discussed.

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OVERVIEW OF DUAL DIAGNOSIS

Substance use disorder—the abuse of or dependence on substances—is common among patients diagnosed with schizophrenia. The primary substances of abuse include alcohol (the most common), cannabis, and cocaine.[1–7] According to the Epidemiologic Catchment Area (ECA) study,[8] the lifetime prevalence of substance use disorder (e.g., with alcohol or other substances) in patients with schizophrenia is 47%, a rate approximately 3 times the background rate in the general population. Alcohol use disorder itself is found in 34% (3 times the rate of the general population), and any other substance use disorder occurs in 28% of these patients (6 times the rate of the general population). In addition, nicotine use is also very common. Studies suggest that 75% to 90% of patients with schizophrenia smoke tobacco, as compared with approximately 21% of the general population.[9]

The high rate of substance use disorder is not found only in patients with chronic schizophrenia; a number of studies have indicated that it is very common in patients early in the course of the disorder.[10–12] For example, a recent study[11] of pharmacologic treatment for patients in their first episode of schizophrenia, which specifically excluded patients in whom recent substance use could have confused the actual diagnosis of schizophrenia, found that 37% of 262 first-episode patients (recruited from sites throughout North America and Europe) had a history of substance use disorder. In this study,[11] 28% of the patients had a lifetime

diagnosis of cannabis use disorder, and 21% had a lifetime diagnosis of alcohol use disorder. For more information on the presence of this comorbidity, please refer to Buckley[13] in this supplement.

COMPLICATIONS OF COMORBID SUBSTANCE USE DISORDERS

According to a study by Hambrecht and Hafner,[10] patients with schizophrenia and comorbid substance use disorders tended to have an earlier age at onset of schizophrenia than patients who did not use substances (the age at onset was 17.7 years of age versus 25.7 years of age, respectively). In another study[11] of first-episode schizophrenia, a history of cannabis use disorder was associated with an earlier age at onset of schizophrenia (by approximately 2 years). Moreover, in this study, the patients with a history of cannabis use disorder had a poorer response to acute treatment than patients without a history of cannabis use disorder.

Studies of patients with chronic schizophrenia have also clearly indicated that co-occurring substance use disorder is associated with poorer overall outcome. These dual-diagnosis patients have higher relapse rates,[14–16] more treatment noncompliance,[16,17] poorer overall response to pharmacotherapy,[18] higher hospitalization rates,[14–16,19] increased risk for violence,[20,21] and higher medical costs[22] than those patients with schizophrenia who do not have a co-occurring substance use disorder. Clearly, strategies to limit substance abuse in these patients need to be developed.

NATURE OF SUBSTANCE ABUSE IN SCHIZOPHRENIA

As a general rule, substance abuse is thought to be more common than substance dependence in patients with schizophrenia. Their pattern of use tends to be regular, but the overall amount of use is moderate. However, it is clear that even this moderate use worsens the primary symptoms of schizophrenia and, subsequently, the overall course of the psychosis.[23] Given the difficulties that substance use disorders produce in patients with schizophrenia, there has been considerable discussion in the literature attempting to explain the basis of this association.

One possible theory is that substance use triggers the development of schizophrenia in some individuals. For example, phencyclidine (PCP) use may induce symptoms associated with schizophrenia, including psychosis.[24] Moreover, a number of recent articles have examined the possibility that cannabis use can trigger the onset in those who may be predisposed to schizophrenia.[25] The work of Caspi and colleagues,[26] indicating that adolescent cannabis use is associated with the development of psychosis years later in those individuals with the high output (val/val) form of the gene for catechol *O*-methyltransferase (COMT), demonstrates how this "gene-environment" interaction may actually occur. Most investigators suggest that although some substances (particularly cannabis) may be associated with an earlier age at onset of schizophrenia, substance use itself does not cause schizophrenia.

Another common theory suggests that substance use is a form of self-medication and that the use of substances is an attempt to lessen either positive or negative symptoms of schizophrenia. Khantzian[27,28] and Siris[29] have been the primary proponents of the self-medication theory. Although this theory makes intuitive sense and it is known that use of substances will lessen negative symptoms,[1] it does not appear that self-medication is causally related to substance use in these patients. For example, Buchanan et al.[30] noted that patients with negative symptoms are actually less likely to use substances than other patients with schizophrenia.

Our group[31] has published a neurobiological formulation suggesting that the dysregulated dopamine-mediated mesocorticolimbic network in patients with schizophrenia may underlie their substance abuse. This theory, based on animal research, suggests that this dysregulated network, which subsumes brain reward circuitry, is partially ameliorated by substances of abuse, even while the substance use worsens the overall course of patients with schizophrenia. Thus, according to this formulation, use of substances may transiently allow patients with schizophrenia to experience normal rewards from daily life. Chambers et al.[32] have also published a neurobiological theory consistent with our formulation.

TREATMENT OF DUAL DIAGNOSIS

Although pharmacologic interventions are focused upon in this section, psychosocial interventions are necessary as well to provide complete and effective treatment to dual-diagnosis patients. In integrated dual-diagnosis treatment programs, one treatment team can deliver medication management as well as substance abuse and psychosocial treatment services.

Antipsychotics

Classical or typical antipsychotics, first introduced in the 1950s, are potent dopamine-2 (D_2) receptor blockers. Although these agents have been shown to be useful for the treatment of patients with schizophrenia, their beneficial effects are somewhat limited. Some patients do not respond to these antipsychotics, others cannot readily tolerate them because of side effects, and many patients who respond acutely may lose their response over time. In addition, cognitive deficits and negative symptoms, important parts of the symptom profile of schizophrenia, are not generally ameliorated by these agents. Last, these medications do not appear to decrease substance abuse in patients with schizophrenia, and there is some suggestion that use of these

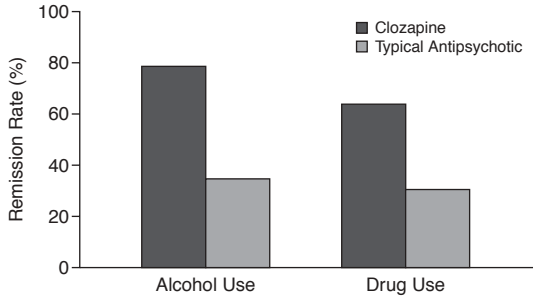
medications may even make substance abuse more likely.[4,5,29,33] For example, McEvoy et al.[33] demonstrated that the use of haloperidol increased the rate of smoking in patients with schizophrenia. Overall, the typical antipsychotic medications appear to be of limited value for controlling substance use or substance abuse in patients with schizophrenia.

There has been hope that the novel or atypical antipsychotic medications may be of greater value than typical antipsychotics in patients with schizophrenia and co-occurring substance use disorder. Although there is considerable controversy about whether the novel antipsychotics are more efficacious than the typical agents,[34,35] the lack of extrapyramidal side effects, the possibility that they are associated with fewer relapses,[36] the possible improvement in some cognitive deficits,[37] and the overall tolerability of these agents have led them to become first line treatments for many patients with schizophrenia.

Of the atypical antipsychotics, clozapine stands out as being the most valuable medication in the treatment of patients with schizophrenia and co-occurring substance use disorders. It is generally considered the most efficacious antipsychotic treatment agent for patients with schizophrenia.[38] Clozapine has been associated with decreased cocaine craving,[39] decreased smoking rates,[40,41] decreased psychosis,[39,42,43] decreased substance use,[42–46] and increased rates of abstinence in these patients.[42,45,46] One study[43] of 29 treatment-refractory patients with dual diagnosis indicated that clozapine reduced psychopathology and improved psychosocial functioning, and semi-structured interviews indicated a decrease in substance use. Drake et al.[44] conducted a naturalistic, longitudinal study of 151 dual-diagnosis, treatment-refractory patients, and the results showed a 79% remission rate of alcohol abuse and a 63% remission rate of drug abuse in patients treated with clozapine (Figure 1). Additionally, a retrospective survey[46] of 36 patients with schizophrenia and active substance use disorder demonstrated that 85% of patients experienced a decrease in substance use and 72% of patients achieved abstinence during treatment. Although case reports and nonprospective studies have suggested clozapine is an efficacious agent, prospective randomized trials are currently being conducted to fully assess the effects of this atypical antipsychotic in dual-diagnosis patients.

My colleagues and I[31] have proposed that although clozapine, like other atypical antipsychotic medications, appears to increase dopamine release in the prefrontal cortex, the unique effects of clozapine in patients with schizophrenia and co-occurring substance use disorders relate to its broad profile of pharmacologic effects. Specifically, clozapine produces weak D_2 receptor blockade, potent noradrenergic α_2 receptor blockade, and a profound release of norepinephrine, which together may be able to improve the signal-detection capacity of the mesocorticolimbic dopamine-mediated circuitry. In essence, then, we have suggested that clozapine may be able to correct (or normalize) the mesocorticolimbic brain reward circuit deficiency that underlies substance abuse in these patients.[31,47]

Figure 1. Remission Rates of Alcohol and Drug Use in Patients With Schizophrenia Treated With Clozapine or a Typical Antipsychotic[a]



[a]Data from Drake et al.[44]

Other atypical antipsychotics include risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. A number of these agents have been studied in patients with dual diagnosis, but there is less information about the effects of these medications than there is for clozapine. In one study,[48] risperidone treatment was associated with decreased cue-related craving, decreased negative and global symptoms, and decreased substance abuse relapses in patients with schizophrenia and comorbid cocaine dependence. However, in a retrospective study[49] of 41 dual-diagnosis patients, abstinence rates (for alcohol and/or cannabis) were substantially higher (54%) in patients treated with clozapine than in patients treated with risperidone (13%).

Olanzapine has been demonstrated to be as efficacious for the treatment of psychosis in patients with schizophrenia and comorbid substance use disorders as it is in patients with only schizophrenia.[50] However, although Noordsy et al.[51] found that patients who switched treatment to olanzapine from typical antipsychotics experienced improvements in their alcohol and drug use as compared with their baseline usage, the same level of improvement was noted in those individuals who remained on typical antipsychotics. Other studies[52,53] have shown that olanzapine may reduce cravings for and use of cocaine in patients with schizophrenia. Last, Littrell et al.[54] reported that olanzapine decreased substance use in 70% of those treated (N = 30). These studies suggest that although olanzapine may have beneficial effects in the dual-diagnosis population, further work is needed to fully understand the extent of those effects.

Among the other atypical agents, quetiapine has been associated with improvement in psychiatric symptoms and with a reduction of stimulant cravings in patients with psychiatric illnesses who switched from typical antipsychotic treatment to quetiapine.[55] Moreover, studies[56,57] of aripiprazole, another atypical antipsychotic, reported that patients treated with this agent had decreased craving for alcohol or

cocaine, decreased use of alcohol or cocaine, and a decreased number of positive drug screens.

Adjunctive Agents

Other agents have been used adjunctively with antipsychotic pharmacotherapy in attempts to treat patients with schizophrenia and substance use disorder, most specifically for co-occurring alcohol use disorder. Although a number of medications have been developed for use in alcohol use disorder, only a few of them have been tried in patients with schizophrenia. Disulfiram has shown some beneficial effects in this population,[58] although there has been some concern about the possibility of an increase in psychosis in patients with schizophrenia taking this agent.[59] Thus, caution is usually advised when using disulfiram with these patients. Naltrexone, an opioid antagonist, has been approved for use in the treatment of alcoholism.[60–64] Petrakis et al.[65] reported that patients with schizophrenia and alcohol use disorder treated with naltrexone in addition to their neuroleptic medication had fewer drinking days, fewer heavy drinking days, and less alcohol craving as compared with baseline assessments, and the adjunctive agent did not affect symptoms of the psychosis. Acamprosate, an agent with apparent glutamatergic effects,[66] has been recently approved for the prevention of relapse to alcohol abuse; however, there do not appear to be any studies that have examined this agent in patients with co-occurring schizophrenia. In addition, topiramate, a medication approved for the treatment of epilepsy, has been recently studied in patients with alcoholism and has shown some intriguing beneficial effects.[67] Once again, there do not appear to be any studies assessing the value of this medication in the co-occurring population of patients with schizophrenia and alcohol use disorder. Last, 1 study, by Ziedonis et al.,[68] assessed the efficacy of desipramine (a tricyclic antidepressant) in patients with schizophrenia and comorbid cocaine abuse; some decrease in cocaine use was reported.

Although it is clear that new medications are being made available for the treatment of alcohol use disorder, few of these have been examined thus far in patients with schizophrenia and co-occurring alcohol use disorder. Future studies are warranted to further elucidate the efficacy of adjunctive medications in dual-diagnosis patients.

CONCLUSION

Substance use disorder in patients with schizophrenia can lead to an exacerbation of the psychosis and a poor long-term outcome. Pharmacologic interventions that can limit the substance use, in both chronic patients as well as in those in the early phases of schizophrenia, are important to develop. Typical antipsychotics appear to be of limited value in controlling the substance abuse in patients with schizophrenia, whereas preliminary studies suggest that some of the atypical antipsychotics, especially clozapine, may be able to decrease substance use in this population. Adjunctive medications, some of which have been recently approved for the treatment of alcohol use disorder, may be helpful in these patients, although research on these agents is in an even more preliminary state than that on the role of atypical antipsychotic agents in this population. Whatever the pharmacologic treatment intervention, however, these dual-diagnosis patients appear to do best in an integrated dual-diagnosis program, in which psychosocial approaches and medication management are delivered by one team specifically trained for this purpose.

Drug names: acamprosate (Campral), aripiprazole (Abilify), clozapine (FazaClo ODT, Clozaril, and others), desipramine (Norpramin and others), disulfiram (Antabuse), haloperidol (Haldol and others), naltrexone (Revia, Vivitrol, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, clozapine, desipramine, olanzapine, quetiapine, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of comorbid substance use disorder and topiramate is not approved for the treatment of alcoholism.

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