Schizophrenia and Comorbid Substance Use Disorder: Effects of Antipsychotics

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The rate of comorbid substance use disorder in patients with schizophrenia is 3 times higher than that in the general population. Men with schizophrenia appear to be particularly vulnerable to substance use disorders. Substances commonly abused in patients with schizophrenia include alcohol, cannabis, and cocaine. Although the basis of comorbidity is unclear, a number of theories have been proposed, including the possibility of a deficiency in the dopamine-mediated mesocorticolimbic brain reward circuit. Data suggest that substance abuse may complicate and worsen the course of schizophrenia. Early intervention with appropriate pharmacotherapy may prove beneficial and potentially improve the long-term course of the disorder. Conventional antipsychotics have not been overly useful in this patient population, but some atypical antipsychotics have been shown to reduce the use of alcohol, cannabis, cocaine, and tobacco in patients with schizophrenia. Further research is required, but early evidence suggests that at least some atypical antipsychotics may prove to be therapeutically effective in the treatment of patients with schizophrenia and comorbid substance use disorder.

(J Clin Psychiatry 2005;66[suppl 6]:21–26)

The clinical presentation of schizophrenia includes 3 core domains: positive symptoms (delusions, hallucinations, disorganized speech, and disorganized or agitated behavior), negative symptoms (anhedonia, limited emotional expression, impaired attention or concentration, and reduced social interaction), and cognitive deficits (particularly in attention and working memory).[1]

Functioning often declines as schizophrenia progresses (Figure 1). The prodromal stage is marked by nonspecific symptoms that may ultimately develop into full-blown schizophrenia. While the appearance of signs and symptoms in the prodrome does not absolutely predict development of schizophrenia,[2,3] at least 2 recent small studies (N = 34[4] and 28[3]) have suggested that 26.5% to 35.7% of patients with possible prodromal symptoms may develop psychotic disorders within the next 6 months or more.[3,4] It is hoped that early intervention may slow the decline in functioning, seen as early as the prodromal stage, potentially altering the long-term course of the disorder. Studies to better define the prodromal phase are in progress.[3]

Substance use disorders (abuse or dependence) are particularly prevalent in patients with schizophrenia, with lifetime estimates of more than 40%.[5,6] The coexistence of schizophrenia and substance use disorder is often referred to as "dual diagnosis." The substances most commonly abused by patients with schizophrenia are alcohol, cannabis, and cocaine.[7] Although tobacco smoking may not be considered a classic substance use disorder, it is also highly prevalent (58%–90%) among patients with schizophrenia compared with the general population (28%–30%).[7]

This review addresses the basis of the comorbidity of schizophrenia and substance use disorder, the treatment challenges faced by patients with dual diagnoses, and the effects of antipsychotic therapy in these patients.

PREVALENCE OF SCHIZOPHRENIA AND COMORBID SUBSTANCE USE DISORDERS

Comorbidity rates for schizophrenia and substance use disorder are difficult to estimate with any certainty. Rates reported in the literature vary considerably, ranging from 40% to 70%,[8] but these differences can be attributed to a number of factors.[9] These include different sampling techniques, differences in diagnostic definitions, and varying patterns of drug use in the general population over time in particular geographic areas.[9] Despite such varia-

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A roundtable for the authors in preparation for this supplement was held December 21, 2002, in Philadelphia, Pa., and was supported by AstraZeneca Pharmaceuticals LP. Editorial assistance with this article was provided by Complete Healthcare Communications, Inc., and supported by AstraZeneca Pharmaceuticals LP.

Dr. Green reports research support from the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Mental Health as well as from Novartis, Bristol-Myers Squibb, Otsuka, Forest, Eli Lilly, and AstraZeneca. Dr. Green has participated in speakers/advisory boards for Eli Lilly, Janssen, and AstraZeneca and has been a consultant for Forest.

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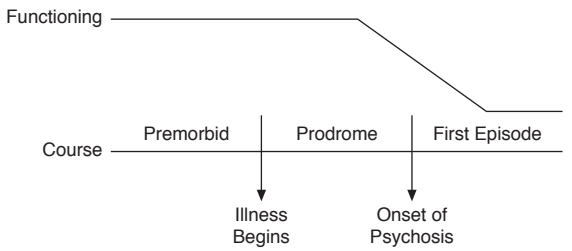
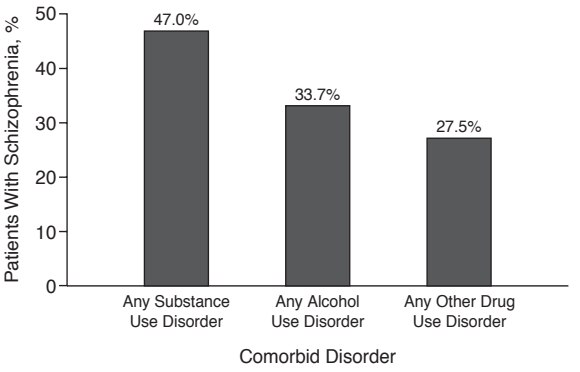
Figure 1. Course of Schizophrenia[a]



[a]Reprinted with permission from Jeffrey A. Lieberman, M.D.

Figure 2. Lifetime Prevalence of Substance Use Disorder in Patients With Schizophrenia[a]



[a]Data from Regier et al.[5]

tions, a clear relationship between substance use disorder and schizophrenia is apparent.[9]

According to the Epidemiologic Catchment Area study data, 47% of people with schizophrenia have a history of some type of substance abuse or dependence (Figure 2),[6,7] a rate nearly 3 times higher than in the general population.[7] Alcohol is the most common substance of abuse in patients with schizophrenia, with a lifetime prevalence rate of 33.7%.[6] The comorbidity rate for other types of drug use disorders is 27.5%.[6]

Substance use disorders are seen in men with schizophrenia more frequently than in women,[9] possibly as a result of gender differences in the presentation and characteristics of schizophrenia. Women with schizophrenia have been shown to experience later onset, better premorbid functioning, fewer negative symptoms, and fewer structural brain and neurophysiologic abnormalities than men with the disorder.[10,11] Gender-related neurodevelopmental differences in the central nervous system structure and function, including neuroprotective effects of estrogen,[11] may also play a role. Yet, in women with schizophrenia and comorbid substance use disorders, unique characteristics that appear to be protective may be compromised. Clinical features in women with schizophrenia and substance use disorder resemble those in men with schizophrenia in terms of disease course, age at onset, hospitalizations, and overall functioning.[10]

Patients with first-episode schizophrenia also are likely to have a high rate of comorbid substance use disorder. In a double-blind, multisite, international 2-year study of olanzapine versus haloperidol in 262 patients with first-episode psychosis,[12] 37% of patients had a lifetime diagnosis of substance use disorder, 28% had a lifetime cannabis use disorder, and 21% had a lifetime alcohol use disorder. In another sample of 232 patients at first admission,[9,13] 23.7% had a lifetime history of alcohol abuse compared with 12.3% of controls, and 14.2% had a lifetime history of drug abuse compared with 7% of controls. Moreover, 88% of patients with drug abuse reported using cannabis.[9,13]

Cannabis is a prominent drug of abuse in patients with first-episode schizophrenia.[8,11,12] Given this finding, it is plausible to hypothesize that cannabis use may advance the onset of first-episode schizophrenia, although reports to date have been somewhat conflicting.[7,12–14]

COMPLICATIONS OF SUBSTANCE USE DISORDER IN SCHIZOPHRENIA

Age at Onset

In general, alcohol use disorder follows the first manifestations of schizophrenia in that it is similar in time of onset to that of negative symptoms but precedes the onset of positive symptoms.[9] In a retrospective study, Tsuang et al.[15] found that the age at onset of psychiatric symptoms was earlier in patients with schizophrenia and comorbid substance abuse than in patients with schizophrenia alone. Cannabis use disorder has also been associated with early age at onset of schizophrenia.[12,14]

Relapse and Hospitalization

Several reports suggest that patients with schizophrenia and comorbid substance use disorder are more prone to relapse and hospitalization.[7] Some studies have found correlations between substance abuse and positive and negative symptoms of schizophrenia, although no such correlation was found in other studies.[16] Although alcohol and other substances have been shown to lessen negative symptoms, these effects may not be causally related to the substance abuse.[7,17] Frequent cannabis and cocaine use can also temporarily increase positive symptoms.[16] Other factors that contribute to morbidity in patients with comorbid substance use disorder and schizophrenia include noncompliance with treatment, social difficulties, and heightened risk of infection.[8] In a study of hospitalized patients with and without schizophrenia,[18] the prevalence of recent (6 months or less before hospitalization) drug use was significantly higher in patients with schizophrenia than in those without the disorder. The use of stimulants appeared

to worsen active psychosis in patients with schizophrenia whether or not they were taking antipsychotic medication.[18] Cocaine use, in particular, has been suggested to worsen the clinical course of schizophrenia, exacerbating many of the symptoms of the disorder and resulting in relapse and increased need for hospitalization.[19]

Treatment Noncompliance and Poorer Overall Response

Higher rates of noncompliance with treatment regimens occur in patients with schizophrenia who have substance use disorder.[16,20] In a longitudinal outcome study of 135 patients with schizophrenia,[20] patients with current substance abuse were 8 times more likely to report medication noncompliance than those without substance abuse.[20] The combination of noncompliance with treatment and substance abuse also results in poorer outcomes.[20]

Studies indicate that patients with schizophrenia and comorbid substance use disorder are more refractory to treatment with antipsychotic medications, even early in the course of schizophrenia. Bowers et al.[21] found that young men with a history of drug abuse in trials using fixed-dose antipsychotic protocols had a poorer early response than young men with psychosis and no history of drug abuse. Similarly, Green et al.[12] reported that patients with first-episode schizophrenia and comorbid substance or alcohol use disorders were less likely to respond to antipsychotic treatment than patients without such comorbidities.

Increased Risk of Violence and Suicide

Individuals with schizophrenia and comorbid substance use disorder may also be at increased risk for violent behavior. Swanson et al.[22] reported that these patients are more than 3 times as likely to exhibit violent behavior as those with schizophrenia but no history of substance abuse. The risk increased with the number of psychiatric diagnoses. In addition, suicide may also be a potential concern in patients with schizophrenia and comorbid substance use disorder, although it is not completely clear whether substance abuse contributes independently to suicide risk in these patients.[17]

Medical Costs

Costs related to substance use disorder can further increase the financial burden associated with schizophrenia, since patients with schizophrenia who have substance use disorder are much more likely to use health care and social services as both inpatients and outpatients. In one prospective study,[23] patients with current comorbid substance use disorder and schizophrenia used significantly ($p < .05$) more institutional services and were twice as likely to visit emergency rooms than patients with no history or evidence of substance use disorder. In a cross-sectional study,[24] patients with a major mental illness (e.g., schizophrenia) and substance abuse had substantially higher psychiatric treatment costs than patients without comorbid substance abuse.

BASIS OF COMORBIDITY OF SUBSTANCE USE DISORDER AND SCHIZOPHRENIA

A number of theories have been proposed to explain the high rates of comorbidity between schizophrenia and substance use disorder. A vulnerability hypothesis suggests that substance use disorders could precipitate the onset of schizophrenia.[9] The self-medication model suggests that patients with schizophrenia engage in abuse because their substances of choice may relieve distressing symptoms of schizophrenia or unpleasant adverse events associated with treatment.[7,9,25] This model is partially supported by findings that many of the negative symptoms of schizophrenia, such as lack of motivation and anhedonia or the neurologic adverse effects of antipsychotics, are lessened, although positive symptoms can be aggravated, by self-medication.[7,25,26] While this theory is plausible, other studies have shown that first-episode patients (who may not be taking antipsychotics) and those with few negative symptoms are also likely to use substances of abuse.[7,17]

A neurobiological hypothesis suggests that a deficiency in the dopamine (DA)-mediated mesocorticolimbic brain reward circuit may underlie substance abuse in patients with schizophrenia.[7,17,27] The mesocorticolimbic dopaminergic pathways, which are thought to be dysregulated in patients with schizophrenia,[26] may underlie both positive and negative symptoms as well as the reward deficiency. Substances such as alcohol, cannabis, and cocaine may transiently ameliorate the deficiency in the brain reward circuit by increasing the efficiency of key DA pathways, but they can also worsen the course of schizophrenia by exacerbating positive symptoms.[17,26]

TREATMENT OF PATIENTS WITH SCHIZOPHRENIA AND COMORBID SUBSTANCE USE DISORDER: THE ROLE OF ANTIPSYCHOTICS

Outcomes evaluated in efficacy studies of antipsychotics in patients with comorbid schizophrenia and substance use disorder include changes in symptoms as well as substance use, quality of life, patient satisfaction, cognitive functioning, restrictiveness of setting, family burden, and use of services. In general, for these dually diagnosed patients, conventional antipsychotics are associated with poor response rates[7,17]; some reports suggest that they may induce or worsen substance use disorders.[28,29] In one study, patients with schizophrenia were shown to smoke more after starting treatment with haloperidol, relative to their baseline rate.[29] Conventional antipsychotics are also associated with a high incidence of neurologic adverse

events in these patients, such as extrapyramidal symptoms, which are thought to increase the likelihood of substance abuse.[7,28]

In contrast to the problems observed with conventional agents, atypical antipsychotics have shown a number of benefits in patients with schizophrenia. These include improved response rates in positive and possibly negative symptoms,[17] fewer relapses,[30] fewer neurologic adverse events,[5,31] improved cognition,[5,32] possible lower rates of suicide and suicidal ideation,[33,34] and a role in alleviating comorbid substance abuse.[17,26,35]

It is believed that conventional antipsychotics may not reduce alcohol or substance abuse in patients with schizophrenia because of their potent dopamine-2 (D_2) blockade, which in part does not allow for restoration of brain reward circuit function.[36–38] In contrast, the atypical antipsychotic clozapine, which has been reported to limit substance abuse in comorbid patients,[35,36] appears to rely less on pure D_2 blockade.[39]

As noted in a review by Noordsy and Green,[36] clozapine has consistently been shown to reduce substance abuse in preliminary studies. A number of preliminary studies in such patients with schizophrenia have shown that clozapine decreases psychotic symptoms, increases the level of functioning, and decreases alcohol and cannabis abuse.[35,40,41] Studies of other atypical antipsychotic agents are even more preliminary. Clinical experience has shown that atypical antipsychotics may reduce cravings for cocaine in patients with schizophrenia. Yovell and Opler[42] reported the case of a treatment-resistant psychotic patient whose cravings for cocaine were reduced with clozapine treatment. In a group of patients with diverse psychiatric illnesses (schizophrenia, bipolar disorder, schizoaffective disorder, and major depressive disorder) and comorbid substance abuse (cocaine and amphetamines), psychiatric symptoms improved and stimulant craving decreased when conventional antipsychotics were discontinued and quetiapine was substituted.[43] Risperidone has also been reported to help reduce cravings and relapses in cocaine-dependent patients with schizophrenia[44] but may not be as efficacious as clozapine for such dually diagnosed patients; a retrospective study of patients with schizophrenia and comorbid alcohol or cannabis use disorder found that treatment with clozapine ($N = 24$) was more likely to be associated with abstinence than treatment with risperidone ($N = 8$) (54% vs. 12.5%, $p = .05$).[41] Olanzapine appears to produce good symptom responses in treatment-refractory schizophrenia and comorbid substance abuse.[45] Case reports and uncontrolled studies suggest that olanzapine may also reduce cocaine craving and use in patients with schizophrenia,[46–48] although one study suggested its effect on substance use was similar to that of typical antipsychotics.[49]

Clinical trials and anecdotal reports propose that atypical antipsychotics can decrease smoking in patients with schizophrenia.[50–52] In a 10-week study,[53] atypical antipsychotics (quetiapine, risperidone, olanzapine, and clozapine) were compared with typical antipsychotics in 45 patients with schizophrenia who were also using a nicotine transdermal patch for smoking cessation. More than twice as many patients in the atypical antipsychotics group (55.6%) stopped smoking compared with the group taking typical antipsychotics (22.2%).[53]

Clearly, further studies are required to fully elucidate the effects of atypical antipsychotics in patients with schizophrenia and substance use disorder.

CONCLUSION

Substance use disorder is a common comorbid condition in patients with schizophrenia.[6,7,13] The presence of substance use disorder further complicates the management of patients with schizophrenia not only by increasing medical costs and the risk of relapse and hospitalization but also by further increasing the risk of treatment noncompliance, violent and possibly suicidal behavior, and treatment refractoriness. In addition, drug abuse may precipitate the early onset of schizophrenic symptoms.[13–15]

Although the basis of comorbidity of substance use disorder and schizophrenia is unclear, we[26] and others[27] have proposed a neurobiological model to explain the high rates of comorbidity between schizophrenia and substance use disorder. This theory, based on the neurodevelopmental and neurodegenerative models of schizophrenia, suggests that a hypoactive mesocortical DA pathway, coupled with a hyperactive mesolimbic DA pathway, produces dysregulation of the brain reward circuit in patients with schizophrenia and comorbid substance use disorder. We have proposed that substances of abuse transiently ameliorate the deficiency in the brain reward circuit and thus help patients feel somewhat better. However, substances of abuse can also worsen the course of schizophrenia.[17,26]

As our knowledge about the neurobiological basis of schizophrenia and substance use disorder increases, it reinforces the need to provide early treatment intervention in an attempt to alter the long-term course of schizophrenia. Antipsychotic therapy that is capable of improving the symptoms of schizophrenia and also reducing substance abuse would be expected to provide the most benefit to patients with schizophrenia and comorbid substance use disorder. This appears to be the case with clozapine and possibly other atypical antipsychotics. Unlike conventional antipsychotics, which are potent D_2 blockers, atypical antipsychotics that produce a relatively weak blockade of D_2 receptors or act at multiple neurotransmitter sites may have a beneficial effect in patients with comorbid substance abuse.[36] This has especially been the case with clozapine,[26,35,40–42,54] but preliminary data with quetiapine,[43,55] olanzapine,[36,45] and possibly risperidone[44] also suggest a potential benefit. Although this

research is in the preliminary stages, management of these patients with atypical antipsychotics may prove to be an important and effective treatment strategy. As clinicians begin to recognize the importance of providing earlier treatment intervention in patients with schizophrenia and comorbid substance use disorder, the need for an effective treatment strategy in this patient population, including the role of antipsychotic medications, becomes all the more important.

Drug names: clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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