Substance Abuse in Schizophrenia: A Review

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Approximately half of the patients who suffer from schizophrenia are also substance abusers at some time during their illness. The motivational drive toward abusive consumption is compounded in individuals with schizophrenia who turn toward substances with reinforcing properties to alleviate aspects of psychosis. This review examines the prevalence, etiology, and clinical effects of substance abuse (e.g., alcohol, nicotine, cocaine) among individuals with schizophrenia. Clearly, substance abuse persists despite and in spite of treatment with typical antipsychotics. The efficacy of newer generation antipsychotics in the reduction of substance abuse among the schizophrenic population has yet to be established, but clozapine has been shown to reduce alcohol, smoking, and cocaine use. Hence, clozapine is a therapeutic option for dually diagnosed patients because of its superior efficacy relative to conventional neuroleptics and its capacity to control substance abuse.

(Please note: The text continues with additional information on substance abuse in schizophrenia, including precipitating factors, prevalence, etiology, and clinical effects of various substances such as alcohol, nicotine, and cocaine. The text also discusses the role of antipsychotics, genetic vulnerability, and other factors influencing substance abuse in schizophrenia.)
former psychotic inpatients use alcohol primarily for its euphoric, antidepressant, or relaxing effects.\textsuperscript{11-14}

In examining the chronology of substance abuse and schizophrenia, Hambrecht and Häfner\textsuperscript{14} reported that alcohol abuse and drug abuse occurred before the onset of symptoms in 24% and 14%, respectively, of a first-episode sample of 232 schizophrenic patients. Alcohol abusers have been noted to have more florid symptoms, more rehospitalization, and a poorer long-term outcome.\textsuperscript{13}

### Nicotine

Whereas approximately one quarter of the U.S. population are smokers,\textsuperscript{15} patients with schizophrenia have a disproportionately high incidence of smoking. Some reports cite that more than 70% of patients with chronic schizophrenia are nicotine dependent.\textsuperscript{5,16} The extent of this problem is most evident in those patients with severe and persistent mental illness, especially those requiring long-term residential care.\textsuperscript{17} Thus, the high proportion of smoking raises concern not only because of the harmful effects of cigarette smoke per se, but also because smoking may serve as a “gateway” to abuse of other substances.\textsuperscript{5,16} However, the relationship between smoking and schizophrenia is complex, and the smoking may attenuate ill effects or neuroleptic effects, or both.

Patients with schizophrenia who smoke have demonstrated improvement in negative symptoms.\textsuperscript{18} In addition, an analysis of auditory-evoked potentials suggests that nicotine improves the processing of auditory data in schizophrenic patients.\textsuperscript{19} The elevated smoking rate among patients with schizophrenia may be due, in part, to heightened nicotine withdrawal symptoms that these patients can experience.\textsuperscript{5}

### Cocaine

Cocaine is a stimulant widely abused in society, particularly by persons with mental disorders. The lifetime prevalence for cocaine abuse among patients with schizophrenia is between 15% and 50%.\textsuperscript{20,21} It has been suggested that some patients who abuse cocaine may actually have a less severe form of schizophrenia that is worsened by cocaine abuse. Cocaine abusers without a primary diagnosis of schizophrenia are likely to, in addition, have severe drug and alcohol abuse, addiction-related psychosocial impairment, antisocial behavior, and comorbid psychiatric problems.\textsuperscript{22} It has also been reported that cocaine may reduce both positive and negative symptoms of schizophrenia and is often taken by psychiatric patients to relieve feelings of depression.\textsuperscript{12}

### CLINICAL EFFECTS OF SUBSTANCE ABUSE

Although substance abuse may provide acute relief from neuroleptic-induced side effects, such habituation has negative long-term effects on the management of schizophrenia (Table 1).

<table>
<thead>
<tr>
<th>Substance Abuse in Schizophrenia</th>
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<tr>
<td>Earlier onset of schizophrenia</td>
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<tr>
<td>Psychotic relapse</td>
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<tr>
<td>Poorer functioning</td>
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<tr>
<td>Greater propensity for violence</td>
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<tr>
<td>Neuroleptic refractoriness</td>
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<tr>
<td>Noncompliance with medication</td>
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<td>Tardive dyskinesia</td>
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Substance abuse is associated with an earlier onset of schizophrenia and poor clinical function.\textsuperscript{23} In 2 independent studies, heavy marijuana abuse was reported to precede the onset of psychotic symptoms by at least 1 year in 42% and 69% of the patients.\textsuperscript{24,25} Another study found that drug abuse preceded (28%) or occurred within a month (35%) of the appearance of the first symptom of schizophrenia.\textsuperscript{14}

D’Mello and colleagues\textsuperscript{26} found that patients with schizophrenia who are substance-abusing tend to receive higher doses of antipsychotic medications. In a clinical trial of conventional antipsychotics in schizophrenic patients with and without a history of substance abuse, Bowes and colleagues\textsuperscript{27} reported a poor treatment response in substance-abusing patients. They postulated that such neuroleptic refractoriness may be due to substance-induced alterations in mesolimbic dopaminergic systems.

Noncompliance with prescribed medication is a serious impediment to the effective treatment of schizophrenia and is even more problematic among patients with a dual diagnosis.\textsuperscript{28} Owen and coworkers\textsuperscript{28} noted that substance abusers with schizophrenia had no contact with healthcare providers, were noncompliant with medication, and had significantly greater symptom severity after 6 months. In another study of 42 schizophrenic inpatients, 57% admitted to drinking alcohol in the month before admission.\textsuperscript{29} The majority of these patients (72%) were noncompliant with prescribed medication prior to hospital admission, and 62% of these patients reported being noncompliant specifically when drinking alcohol. Ironically, dually diagnosed patients may deliberately choose to be medically noncompliant, based on a treatment philosophy among drug abusers that espouses self-reliance, thereby precluding potential benefits of psychotropic medications. It is hardly surprising, then, that patients with schizophrenia who are substance abusers are predisposed to psychotic relapse. Gupta and colleagues\textsuperscript{30} found that active substance abuse in such patients was highly related to readmission rates due to symptom recurrence. This finding was corroborated in a study by Swofford et al.,\textsuperscript{31} which found that substance-abusing patients had 4 times more relapses of schizophrenia over 1 year than did nonabusing patients.\textsuperscript{31} These findings accord well with clinical practice, although the complexity of this association, and possibly causation, between recent drug use and hospitalization is unclear but...
Table 2. Factors That May Enhance the Therapeutic Efficacy of Clozapine and Other Novel Antipsychotics in the Treatment of Comorbid Substance Abuse in Schizophrenia

<table>
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<th>Low propensity for:</th>
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<td>extrapyramidal side effects</td>
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<tr>
<td>tardive dyskinesia</td>
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<tr>
<td>neuroleptic-induced dysphoria</td>
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<tr>
<td>Fewer negative symptoms</td>
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<tr>
<td>Altered mesolimbic dopaminergic tone (attenuation of craving?)</td>
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<tr>
<td>Selective antagonism of central serotonergic receptors (attenuation of craving?)</td>
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<tr>
<td>Psychosocial improvements may assist social skills</td>
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<tr>
<td>Increased medical monitoring may enhance therapeutic alliance</td>
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<td>Weekly blood monitoring during clozapine therapy enables detection of noncompliance and relapse of substance abuse</td>
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is unlikely to be mediated solely by medication noncompliance.32

Recent studies have shown that alcohol can not only exacerbate psychosis but may also accelerate the appearance of TD.33,34 Bailey and coworkers35 examined 1027 patients with schizophrenia and found a very high correlation between substance abuse and diagnosis of TD. A comparative analysis of the prevalence of TD among 51 outpatients with schizophrenia (drug users and nonabusers) treated with antipsychotics revealed that weekly marijuana use was the best predictor for the appearance of TD.36 Indeed, substance abuse may be an independent risk factor for movement disorders.10

REDUCTION OF SUBSTANCE ABUSE WITH NOVEL ANTIPSYCHOTICS

The enhanced efficacy of novel antipsychotics and their low propensity for EPS, in tandem with a potentially advantageous neurochemical profile, suggest that patients with schizophrenia who also abuse drugs may benefit preferentially from treatment with these agents.37 Most evidence of this effect is based on experience with clozapine therapy and, thus far, there is insufficient information on the clinical efficacy of other atypical antipsychotics in this patient subgroup. Possible factors underlying this clinical advantage of clozapine and novel antipsychotics are highlighted in Table 2.

Marcus and Snyder38 found that 85% of 13 schizophrenic smokers treated with clozapine reported either a reduction or cessation of smoking since taking clozapine. These patients did not attribute their decrease in smoking to a reduction in cigarette craving, but rather to an enhanced ability to plan and budget, to a concern over cost of cigarettes, or to a concern over health. These stated reasons reflect clozapine-related improvements in primary psychiatric symptoms. In another study that measured smoking rates in patients who changed from haloperidol to clozapine, smoking was decreased by 25% to 35% in patients with plasma clozapine levels greater than 200 ng/mL,39 suggesting a direct drug-related effect on smoking.

Albanese et al.40 reported case studies of patients with treatment-resistant schizophrenia who chronically abused alcohol. After clozapine administration, the patients exhibited a dramatic decrease in paranoia, became more sociable, and subsequently abstained from alcohol. In another study, Frankenburg41 reported that 50% of schizophrenic patients with comorbid alcohol abuse had stopped drinking within 18 months after clozapine treatment.2

Preclinical and clinical data suggest that clozapine also reduces cocaine-seeking behavior. Kosten and Nestler42 found that clozapine attenuates cocaine-conditioned place preference in rats. In addition, whereas low doses of typical antipsychotics increase stimulant self-administration, clozapine produces a dose-dependent decrease in cocaine intake in rats.43 Vanover and colleagues44 also noted a partial decrease in reinforcing and discriminative effects of cocaine in 50% of tested monkeys.

In one case study, decreased cocaine use after clozapine therapy was reported in a treatment-resistant 37-year-old man with schizoaffective disorder.45 The patient demonstrated resolution of psychosis, improved social function, and a decreased need to use cocaine or other substances. There are other reports of dramatic cessation of substance abuse, attenuated craving, and improved psychosocial function during clozapine therapy.46 In a study of substance abuse among patients with treatment-refractory schizophrenia, a comparable level of efficacy was observed in substance abusers and nonabusers after 6 months of clozapine treatment.46 The results of this study indicate that the poor clinical response that is characteristic of drug-abusing schizophrenic patients may be improved with clozapine treatment. The data also suggest that a craving for illicit drugs may diminish with clozapine therapy.

There are, as yet, no published clinical trials on the efficacy of risperidone, olanzapine, or quetiapine in this patient population. Conley and colleagues47 have recently presented data showing that olanzapine may be an effective treatment for patients with schizophrenia who have a history of substance abuse. Further studies of these novel antipsychotics in dual-diagnosis patients are warranted.

MECHANISM OF ACTION OF CLOZAPINE IN SUBSTANCE ABUSE

The pharmacologic mechanisms underlying the reduction in substance abuse during clozapine treatment are presently unresolved. However, such mechanisms presumably involve the mesolimbic dopamine system, which is associated with motivational states and is implicated in reinforcing the actions of most drugs of abuse.48 Drugs with reinforcing properties (e.g., nicotine, alcohol, cocaine) increase extracellular dopamine levels in humans.49 The decrease in smoking observed in schizophrenic patients taking clozapine, for example, may be due to its
ability to substitute for nicotine by augmenting dopamine release. Criswell and colleagues\textsuperscript{50} reported that clozapine displayed both D\textsubscript{3} and D\textsubscript{2} receptor antagonism in rats hypersensitive to dopamine agonists. These researchers concluded that the greater affinity of clozapine for D\textsubscript{3} and lesser affinity for D\textsubscript{2}, relative to typical antipsychotics, may play a role in modulating the activity of receptors involved in drug craving.

The therapeutic efficacy of clozapine is thought to derive not only from its unique pharmacologic profile but also from the totality of the treatment regimen. The mandatory visits for blood monitoring,\textsuperscript{51} required primarily as a safety measure, have an auxiliary benefit of forming a therapeutic alliance between patient and healthcare professional.\textsuperscript{37} This frequent contact also provides an important psychotherapeutic context to pharmacotherapy.

THE COST OF SUBSTANCE ABUSE IN SCHIZOPHRENIA: THERAPEUTIC IMPLICATIONS

Significant morbidity in the United States is attributed to mental illnesses and substance abuse, ranking third for personal healthcare expenditures.\textsuperscript{52} Schizophrenia, in particular, is a major economic burden, with schizophrenia-related expenditures over $30 billion in the United States for both direct and indirect costs.\textsuperscript{53} Comorbid substance abuse further increases the cost of care, because during periods of alcohol and/or illicit drug use, patients with schizophrenia become severely ill, resulting in symptoms that are more difficult to manage.\textsuperscript{2} Schizophrenic patients who are substance abusers are frequent users of psychiatric and emergency services.\textsuperscript{54} Moreover, dually diagnosed individuals are more likely to be unemployed and possibly homeless, drawing further on community service costs.\textsuperscript{55} Also, some patients use disability payments to support their drug habits.\textsuperscript{56} The lack of income to support the expense of drug abuse may be a precipitating factor leading some to crime and violence.

COST-EFFECTIVENESS OF CLOZAPINE

It is important that the economic disadvantages of comorbid substance abuse are highlighted and juxtaposed with current pharmacoeconomic perspectives on schizophrenia, particularly if it is asserted that novel antipsychotics should be used in this patient subgroup. Although more rigorous, prospective, pharmacoeconomic data are awaited, current evidence suggests that novel antipsychotics can, in spite of higher up-front prescription costs, save money in the long run.\textsuperscript{55,57,58} Several studies attest to the cost-effectiveness of clozapine in treatment-refractory schizophrenia, particularly in the second year of therapy and thereafter. Meltzer and colleagues\textsuperscript{59} have reported substantial cost savings attributable to clozapine therapy, mainly in reduced hospitalization. Of particular relevance to issues of treatment compliance and recidivism among substance abusers are the data showing substantial cost savings accrued when patients continued with clozapine therapy rather than discontinued. It has been argued that, in an era of resource allocation, resources should be focused on effective treatment for those patients who consume a disproportionate amount of health care dollars.\textsuperscript{53,60}

CONCLUSIONS

Comorbid substance abuse in schizophrenia is a common and significant clinical dilemma. In many cases, substance abusers are noncompliant and therefore tend to be high users of emergency (and other) services, primarily because of psychotic relapse. Noncompliance and substance abuse are likely to be aggravated by patients’ experience of neuroleptic-induced side effects such as EPS and neuroleptic dysphoria. Available evidence suggests that clozapine may reduce substance abuse among patients with schizophrenia. This potential benefit, allied with symptom reduction and improvement in overall psychosocial functioning, may result in a reduced risk of psychotic relapse and need for hospitalization, with consequent economic advantage. Additional studies are required to address these issues further, to explore the biochemical correlates of attenuated craving, and to determine whether these benefits also occur with other novel antipsychotics.

\textit{Drug names:} clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroqueul), risperidone (Risperdal).
42. Conley R, Gale E, Hirsch K. Olanzapine response in therapy-refractory schizophrenia with substance abuse (SA) [abstract]. Schizophr Res 1997;24:190