Substance Abuse and Schizophrenia: Editors' Introduction
by Thomas R. Kosten and Douglas M. Ziedonis

Abstract
Most individuals with schizophrenia have problems with abuse of substances ranging from licit substances, such as nicotine, to illicit ones, such as cocaine. This comorbidity may reflect self-medication, as well as a biological susceptibility to both disorders. Twin studies have suggested that this biological susceptibility may involve genetic factors. Other biological risk factors may involve the medications used to treat schizophrenia, which may produce symptoms that provoke abuse of drugs to relieve negative symptoms or may even enhance the euphoric response to abused drugs. The articles in this issue address several research areas related to substance abuse and schizophrenia, including the differential diagnosis of schizophrenia and organic disorders induced by substance abuse and the impact of substance abuse on the course of early schizophrenia. The management of substance-abusing schizophrenia patients requires a careful balance of pharmacotherapy and psychotherapies, and atypical antipsychotic agents may be particularly helpful. Psychotherapy needs to focus both on the management of affect and on the adequate monitoring of drug abstinence.


Several recent studies have demonstrated that up to 50 percent of individuals with schizophrenia have either alcohol or illicit drug dependence, and about 70 percent or more are nicotine dependent (Andreasson et al. 1987; Brady et al. 1990; Dixon et al. 1991; Shaner et al. 1993; Ziedonis et al. 1994). This high rate of comorbidity with substance abuse reflects the influence of risk factors ranging from genetic vulnerability to prominent negative symptoms to medication side effects to psychosocial factors, such as low socioeconomic status, living with other users, and chronic life stressors. The substance abuse may also exacerbate schizophrenia and precipitate psychotic episodes. Although a self-medication hypothesis has suggested that the use of drugs may acutely ameliorate some negative and positive symptoms of schizophrenia, the chronic effect of these abused drugs is detrimental to the psychological well-being of these patients (Khantzian 1985). This detrimental effect may simply be the consequence of noncompliance with antipsychotic agents, but it can also reflect the direct neurochemical effects of stimulants, hallucinogens, or alcohol in precipitating psychotic symptoms. Biological susceptibility to both substance abuse and schizophrenia may be an important factor in these direct neurochemical effects of abused drugs such as alcohol and may be related to a shared genetic predisposition for both disorders.

Genetic factors have been linked to both alcoholism and schizophrenia (Rimmer and Jacobsen 1977; Gottesman and Shields 1982; Goodwin 1983), but little research has assessed the etiological role of genetic factors when the disorders occur together. A twin study by Kendler (1985) provided some provocative data on this comorbidity by addressing two possible roles played by genes in this association. First, although Freed (1975) focused on the role of certain life stresses being associated with both disorders in his review of the literature on co-occurring alcoholism and schizophrenia, the data by Kendler do not support a strong correlation between the environmental precipitants of these two disorders. The diagnoses of schizophrenia and alcoholism were uncorrelated in the cotwins of the monozygotic (MZ) index twins, indicating that the specific environmental factors of causal importance in the two disorders are not related closely.

Second, in individuals with both disorders, genetic factors were not simply important for schizophrenia alone or for alcoholism alone. For example, individuals genetically predisposed to schizophrenia did not then develop...
alcoholism as self-medication or as a means of coping with the anxiety related to their psychotic symptoms. Since the age at onset for schizophrenia preceded the diagnosis of alcoholism in only about half the twins, with no difference between the dizygotic (DZ) and MZ twins, a simple self-medication hypothesis of alcoholism for schizophrenia symptoms was not plausible for about half the patients in this study. (However, see the Khantzian (1985) self-medication hypothesis described later.) Furthermore, based on these twin studies, individuals predisposed to alcoholism and abuse of other drugs such as hallucinogens were not simply prone to develop schizophrenia-like symptomatology, such as auditory hallucinations and persecutory delusions (Victor and Hope 1958). Instead, these 34 MZ and 47 DZ twins with diagnoses of both alcoholism and schizophrenia had a genetic predisposition to both disorders similar to that which causes the two to occur alone.

This final finding indicates a shared genetic predisposition to both disorders. Since both disorders are most likely polygenic in inheritance, they may stem from the same abnormalities in several genes, such as those regulating dopamine or serotonin receptors or metabolism in neurons. Future genetic linkage studies should address this issue.

Another potential biological risk factor involves the medications that are used to treat schizophrenia. Although acute neuroleptics may diminish some of the effects of abused drugs, particularly stimulants, the chronic effects of neuroleptics seem to enhance these same reinforcing properties. Recent studies in rodents have demonstrated that chronic treatment with haloperidol increases the reinforcing effects of cocaine (Kosten and Nestler 1994). This experimental observation in animals is consistent with patient reports about why they abuse cocaine and other drugs. Psychotic patients often report substantial euphoria from relatively modest dosages of cocaine, even while still continuing their neuroleptics. The mechanism of this enhanced response is presumably due to upregulation of the postsynaptic receptor for dopamine secondary to chronic neuroleptic blockade. Other anecdotal human work and human experimental studies further suggest that acute neuroleptic treatment does not reduce the positive euphoric qualities of cocaine, but may in fact only reduce the dysphoria and paranoia-inducing aspects of stimulant use (Gawin 1986; Sherer et al. 1989). Furthermore, schizophrenia patients who abuse stimulants and marijuana frequently report relief of the negative symptoms of schizophrenia and amelioration of the dysphoric effects of neuroleptics (Schmeier and Siris 1987; Brady et al. 1990; Kelly et al. 1992; Albanese et al. 1994; Serper et al. 1995). Negative symptoms of schizophrenia are not well relieved by typical neuroleptics. However, the new atypical neuroleptics (e.g., clozapine, risperidone) may offer an important alternative. The article by Therese Kosten (1997, this issue) reports on recent studies with rodents that suggest the potential clinical utility of these agents for cocaine abusers. Finally, the efficacy of neuroleptics may be compromised by induction of their metabolism by nicotine in those 70 percent or more of individuals with schizophrenia who are nicotine dependent (Pantuck et al. 1982).

In summary, a variety of biological interactions may occur between neuroleptics and abused drugs. These interactions may potentiate the effects of abused drugs, thereby increasing their reinforcing properties. These interactions may also decrease the efficacy of neuroleptics directly via metabolic induction or indirectly through lack of compliance with neuroleptics. Poor compliance by substance-abusing schizophrenia patients commonly precedes an exacerbation of their psychosis and subsequent hospitalization.

When assessing patients with psychotic symptoms and substance abuse, an accurate diagnosis is essential. A variety of abused substances ranging from marijuana to alcohol can induce transient psychotic states that are not indicative of an underlying schizophrenic disorder. The article by Rosenthal and Miner (1997, this issue) examines the important indicators differentiating schizophrenia from a drug-induced psychosis, including the types of psychotic material elicited from the patient. An important correlate of an accurate diagnosis is appropriate use of psychiatric treatment resources, including avoiding hospitalization in those patients who can make an adequate recovery while being held for 1 to 2 days in the emergency room. An accurate diagnosis also enables understanding of the longer-term implications for the course of substance abuse in individuals appropriately diagnosed with schizophrenia.

Patients with schizophrenia who are being treated in mental health settings often have undetected substance abuse. Routine urine testing in triage settings and during periods of poor clinical response is important (Shaner et al. 1993). Important clinical clues of substance abuse include legal problems, episodic homelessness, poor treatment compliance, and recurrent use of the emergency room or need for rehospitalization.

Another important clinical clue to substance abuse is cigarette smoking, especially heavy smoking of more than 25 cigarettes per day. In this journal, Ziedonis and George (1997, this issue) review nicotine use and schizophrenia. Nicotine is a potent drug that alters psychiatric symptoms and medication blood levels, and nicotine use is a gateway to other substance abuses.
The impact of substance abuse on the course of early schizophrenia is examined in depth by Kovaszny and colleagues (1997, this issue), who critically compare substance abusers that have schizophrenia with substance abusers who have affective disorders. Affective disorders are the major psychiatric comorbidity seen among substance abusers, who have rates of lifetime affective disorder ranging from 30 to 60 percent. The rate of schizophrenia in substance abusers is substantially lower and not significantly greater than community rates of schizophrenia, which are about 1 percent (Rounsaville et al. 1982; Regier et al. 1990). As indicated earlier, however, the 50 percent rate of substance abuse in individuals with schizophrenia is substantially higher than community rates of substance abuse. A recent study demonstrated that, over the lifetime course of affective disorders, substance-abusing and nonabusing patients tend to have equivalent rates of depressive relapses, but the substance abusers recover from the depressive relapses more slowly and are less readily responsive to treatments (Mueller et al. 1994). Ries and Comtois (1997, this issue) carefully demonstrates no difference in outcome for those patients with or without substance abuse during their first episode of depression. In contrast, substance-abusing schizophrenia patients have significantly worse 6-month outcomes than nonabusing schizophrenia patients. Thus, even in the early course of the illness after the first hospitalization, schizophrenia patients already experience the detrimental effects of substance abuse.

The poor outcome with standard treatments in substance-abusing schizophrenia patients may be improved by a variety of psychosocial and medication interventions. Ziedonis and Trudeau (1997, this issue) report poor motivation to quit using substances and suggest a dual-diagnosis treatment-matching strategy based on motivational level, type of substance, and severity of illness. In addition to the use of motivational enhancement and dual-diagnosis relapse prevention psychotherapies described by Ziedonis and Trudeau, recent clinical data suggest that atypical neuroleptics such as clozapine may help reduce substance abuse (Buckley et al. 1994; George et al. 1995; Hameedi et al. 1995) and facilitate psychosocial interventions (Ziedonis and Fisher 1996). This reduction in substance abuse is consistent with the rodent studies with chronic clozapine administration reviewed earlier in this article (Kosten and Nestler 1994).

Ziedonis and George and (1997, this issue) report on a smoking cessation treatment outcome pilot study for smokers that have schizophrenia. Improved outcomes were seen with the use of nicotine replacement and intensive psychosocial, twice-weekly, individual motivational enhancement therapy and group therapy.

The management of substance abusers with schizophrenia requires a careful balance of pharmacotherapies and psychotherapies. When integrating these two components of therapy, the treatment contact must explicitly include monitoring for continued use of illicit drugs or alcohol. The usual supportive course of psychotherapy for schizophrenia patients includes relatively little limit setting. In contrast, the treatment of a substance abuser involves substantial components of monitoring and limit setting. This monitoring requires, at the very least, weekly urine toxicologies for illicit drugs, such as cocaine and marijuana, as well as breath analysis for alcohol. Patients in intensive outpatient or day treatment programs may have breath alcohol analysis performed daily. They are then given direct feedback in an empathic and nonjudgmental manner about the results of these urine and breath analyses, and the treatment is tailored to facilitate documented abstinence based on these measures. Achieving a goal of abstinence is a process that begins with harm reduction and encouraging treatment compliance; maintaining a therapeutic alliance is critical.

Another aspect of limit setting in treatment involves the approach to intoxicated patients, particularly those participating in group therapy. If patients present for therapy when intoxicated, they are not allowed to participate in the full treatment session because their presence will be significantly disruptive to other patients in group treatment and therapy will not be beneficial to them, whether in a group or individually. Instead, these intoxicated patients need to be seen for a supportive but firm, brief meeting that supports their attempts to reconnect in treatment, but reinforces their limited ability to do therapy in their current state of use or intoxication. During this meeting, clinicians should perform a brief psychiatric assessment of their potential for violence or suicidality, as well as their possible need of referral to the emergency room and hospitalization. If emergency referral is not necessary, then another appointment should be set up with the patient within the next 24 hours when he or she can be seen in a nonintoxicated state. For patients who have not been in therapy for several weeks, an assessment of the need for medical detoxification may also be necessary.

Although this need for monitoring and limit setting is essential for the management of substance abuse, with a schizophrenia patient the amount of confrontation that is used for dealing with drug-seeking behaviors needs to be carefully titrated. Supportive and psychoeducational therapies that have been the mainstay of effective work with schizophrenia patients continue to be extremely useful for the substance-abusing schizophrenia patients. Highly confrontational group processes, which are typically used within therapeutic communities for substance abusers.
with personality disorders, have little usefulness in the treatment of a substance-abusing schizophrenia patient and may precipitate psychotic reactions. The article by Wilkins (1997, this issue) integrates supportive and monitoring interventions for optimal efficacy with the substance-abusing schizophrenia patient.

An important component of the treatment of the psychotic substance abuser is management of affect because of the role that substance abuse has played in what is often called self-medication (Khantzian 1985). From a psychodynamic perspective, many of these patients find it very difficult to manage not only the dysphoria associated with the negative symptoms of schizophrenia or neuroleptic side effects but also the aggressive urges that are frequently magnified during adolescence when initial schizophrenia breaks usually occur. Drugs such as alcohol, sedatives, and marijuana may significantly dampen aggressive urges in these vulnerable adolescents. Drug abuse thereby provides a level of self-care that the individual with schizophrenia finds impossible to muster without those substances.

Khantzian (1985) has argued two key aspects of his self-medication hypothesis: (1) Abused drugs relieve psychological suffering, and (2) there is psychopharmacological specificity in an abuser’s drug preference. The choice of drug is based on its main effects as well as on the individual’s personality organization and inner states of psychological suffering. This psychodynamic perspective emphasizes ego deficits and how an individual discovers his or her preferred drug through experimentation. When the preferred drugs are alcohol and sedatives, the sense of isolation, being cut off, and the related anxious states are relieved by these sedatives' softening of rigid ego defenses (Krystal 1977). In contrast, stimulants appeal to both high- and low-energy types to either augment hypomanic states or energize the bored, depressed schizophrenia patient. In general, substance abusers are considered to experience affects in extremes and therefore use drugs to control these extremes and to regulate painful feelings. Furthermore, subclinical states of distress, not necessarily psychiatric disorders, are the important operatives that govern self-medication. Even among individuals with schizophrenia, Noorsdy et al. (1991) documented that over half experienced a lessening of social anxiety, tension, dysphoria, apathy, anhedonia, and sleep difficulties with alcohol abuse. These patients also reported relief of poor interpersonal relationships (42%) and shyness (40%).

In his formulation of the self-medication hypothesis for schizophrenia, Khantzian has emphasized the negative symptoms of this disorder (Andreasen 1982a, 1982b, 1990). An interesting observation is that individuals with schizophrenia who experience substantial negative symptoms have significantly lower premorbid levels of functioning during childhood and adolescence than those without negative symptoms (Kelly et al. 1992). Significant suffering and poor interpersonal functioning before the onset of schizophrenia could therefore predispose them to abuse drugs and alcohol as self-medication. Thus, self-medication of the prodroma of schizophrenia might be considered important in the association of these two disorders, even before the onset of substantial negative symptoms of schizophrenia. The treatment implication of this hypothesis for the conduct of psychotherapy is the need to shore up affect defenses in these patients, which may explain the poor efficacy of confrontational substance abuse treatments in this population.

In summary, individuals with substance abuse and schizophrenia present as complex clinical cases with multiple etiological factors, including genetic predispositions, negative symptoms of the disorder that elicit self-medication, and neuroleptic-induced side effects. Treatments need to involve multiple modalities of psychotherapy and possibly atypical neuroleptics or other medication augmentation strategies. Management of affects along with adequate monitoring of drug abstinence, is a key to psychotherapy. Clinical work with these individuals is initially demanding, but can be rewarding and stimulating. Realistic treatment goals and skills in appropriate psychotherapy and pharmacotherapy approaches are important to success. Extensive clinical experience indicates that treatment can be helpful; however, research efforts in this area must be continued and supported.

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