Impact of Substance Abuse on the Course and Outcome of Schizophrenia

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Abstract

Numerous pharmacological agents have been shown to have powerful effects on cognitive behavior. Schizophrenia-like reactions have been reported in some instances. There have also been persistent reports of drug abuse among psychiatric patients before and during hospitalization. These phenomena have led to speculation that psychoactive substances are affecting the course and outcome of psychiatric illnesses, and in particular, schizophrenia. This report first reviews the evidence for psychotomimetic effects of various drugs, and then focuses on reports of the effect that substance abuse has on the course of schizophrenia and long-term outcome. The evidence to date indicates that there is a need for a large epidemiological analysis of the interplay between drug abuse and schizophrenia as well as more intensive case studies of afflicted individuals. This discussion concludes with suggestions for improved research methods and two designs for future investigations.

Previous investigations have indicated that psychopathology may increase the incidence of specific types of drug abuse, and drug abuse may exacerbate psychiatric disturbances (McLellan and Druley 1977; Schneier and Siris 1987). Furthermore, psychoactive substances have been implicated in the early onset of psychosis (Breakey et al. 1974; Tsuang et al. 1982).

Psychotomimetic Drugs

There is considerable evidence that certain psychoactive substances can mimic or aggravate psychotic symptoms. This has been viewed as both a benefit (enabling researchers to control and study psychotic episodes) and a hindrance (confounding both the initial assessment of presenting symptoms and the course of treatment) to our understanding of schizophrenia. It also raises questions about the role that drugs may play in augmenting latent schizophrenic disorders in susceptible individuals.

Cole and Katz (1964) examined the psychotomimetic properties of d-lysergic acid diethylamide (LSD), concluding that it produces a “state which is similar but not identical to naturally occurring schizophrenia” (p. 758). They discussed LSD and its derivatives as both obstacles for diagnosis and as therapeutic agents. While there was initial hope that controlled examination of psychotic states might help to understand those similar hallucinogenic states found in schizophrenia, the authors concluded that there is insufficient evidence to support the extensive use of the drugs, but expressed hope that their use in carefully controlled hospital settings could provide insights into the course of schizophrenia. The work of Janovsky and Davis (1976) provides some justification for the use of stimulants as psychodiagnostic agents in view of their ability to enhance psychotic symptoms under controlled conditions, although these authors also advocate more conservative strategies for obtaining

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similar information about schizophrenic symptomatology.

An alternative approach has been to compare the psychotic states produced by hallucinogenic drugs to those reported by drug-free schizophrenic patients. Bell (1965) reviewed published reports of amphetamine psychosis and carefully noted similarities and differences between these and the subjective reports of hallucinations given by schizophrenic patients. The most obvious difference involves the duration of the hallucinations. Drug-induced symptoms usually clear within 10 days of withdrawal from the drug, while schizophrenic hallucinations usually last for months. The quality of the hallucinations is also different, with visual images dominating in the drug-induced cases, which is not common in schizophrenia.

Stone (1973) reviewed the research literature involving the case histories of patients who abused drugs and had schizophrenia. He distinguished between drug-induced drug-aggravated psychoses and drug use that accompanied preexisting schizophreniform reactions. He argued for a multidimensional diagnostic approach to help to distinguish among these possibilities. His schema involved the presence or absence of a series of genetic, constitutional, organic, and psychological factors. The pattern of these factors indicated predispositions to adverse reactions to stimulant drugs.

Negrete et al. (1986) reported an enhancement of psychotic symptoms (delusional and hallucinatory activity) among schizophrenic patients who use marijuana. The authors suggested that the observed effects may be due to (1) an exacerbation of psychotic symptoms, (2) a secondary toxic psychosis superimposed on the schizophrenic state, or (3) a diminution of the effectiveness of the antipsychotic medication that the patients were taking. Once again, the data were insufficient to differentiate between these alternative mechanisms.

O'Brien et al. (1984) reported high frequencies of psychiatric diagnoses among opioid users in treatment, but relatively low levels of psychosis or schizophrenia. McLellan et al. (1979) found psychosis was much more prominent among stimulant users.

Although alcohol is apparently not the drug of choice among schizophrenic patients, its ready availability and licit status make it a frequently abused substance. Schuckit (1983) noted that primary alcoholism can mimic most psychotic disorders, and secondary alcohol abuse can accentuate psychotic symptoms. He advocated for routine psychiatric assessments of all alcoholism patients and, conversely, alcoholism screens for all psychiatric admissions.

Drugs as Precipitants of Psychosis

Investigations of the co-occurrence of drug abuse and schizophrenia should determine the specific substances being abused, as well as the quantity and frequency of abuse. That history must then be temporally related to the course of the psychotic illness. This procedure is essential for determining whether the observed substance abuse among schizophrenic patients (1) precedes the onset of psychopathology and is therefore either a precipitant or a cause; (2) follows the onset of symptoms and may represent an attempt to self-medicate or ameliorate symptoms; or (3) merely accompanies the disorder and is not directly related to the clinical pathology, though it could still affect the course of the illness. Relatively few studies have adequately addressed this problem. Previous findings are equivocal, providing some evidence to support each of the three hypotheses.

Researchers have stressed the increased vulnerability of drug abusers to psychotic episodes. For instance, Hensala et al. (1967) investigated the role of LSD in triggering psychotic episodes and hospitalizations. They examined a broad spectrum of variables, including demographic characteristics, family history, and psychosocial adjustment as well as drug involvement. They concluded that in only 25 percent of the cases investigated was LSD directly related to the index hospitalization. In the remaining cases, poor premorbid adjustment, high-risk family history, and extensive substance abuse were associated with an increased risk for hospitalization.

Breakey et al. (1974) investigated the drug usage and premorbid personality of hospitalized schizophrenic patients and reported that those who used drugs had a significantly earlier age of onset of symptoms. Furthermore, they were more likely to be free of personality disorders before their psychosis than were the nondrug-using psychotic subjects. They concluded that the drugs had a precipitating role among individuals who were "somewhat less constitutionally vulnerable" to schizophrenia (p. 260). Similarly, Tsuang et al. (1982) reported a significantly earlier onset of psychiatric illness and first psychiatric hospitalizations among
long-term drug-abusing psychotic patients when compared to nondrug-abusing schizophrenic or atypical schizophrenic patients.

Bowers and colleagues (Glass and Bowers 1970; Bowers 1972, 1977; Bowers and Swigar 1983; Bowers and Wing 1983) also investigated the premorbid personality traits and family history of long-term hallucinogenic drug users who suffer from chronic psychotic episodes. They concluded that susceptibility to drug-induced psychosis is frequently associated with an early development that is relatively free of personality disturbance (Glass and Bowers 1970; Bowers 1972), but is more likely to be characterized by a reluctance to deal with life stresses (Glass and Bowers 1970). They further noted a genetic predisposition, characterized by increased rates of parental psychiatric disorders (Bowers 1977; Bowers and Swigar 1983). The relationship between male susceptibility to drug-induced psychosis and parental history of psychiatric disorders was found to be reciprocal, such that those “with a positive family history appear capable of becoming psychotic in association with relatively small amounts of hallucinogen use” (Bowers and Swigar 1983, p. 95). An extensive study by Vardy and Kay (1983) found essentially no differences in premorbid personality among victims of LSD psychosis, but extensive family histories of psychosis (13.5 percent), suicides (7.7 percent), and alcoholism (30.8 percent).

**Drug Abuse at Time of Admission**

A number of authors have examined the rates of use and abuse observed at the time of hospital admissions. Crowley et al. (1974) found that more than one-third of a sample of admissions to an adult psychiatric unit of a university hospital reported drug abuse problems, while nearly one-half had psychoactive drugs in their urine at the time of admission. Within their small sample (n = 50), the schizophrenic patients (22 percent) had relatively low rates of drug use. Similarly, Fisher et al. (1975) reported that one-third of their psychiatric hospital admissions (diagnoses not reported) acknowledged previous drug use, and approximately half of the admitted drug users were currently abusing illicit drugs.

Richard et al. (1985) found a relatively low (11 percent) rate of drug use just before hospitalization, similar to the 8 percent found by Crowley et al. (1974). Contrary to the findings of Crowley et al., Richard et al. reported that their schizophrenic patients acknowledged drug use significantly more often than did their nonschizophrenic patients. Cohen and Klein (1970) examined the drug usage and diagnoses of young (under 25 years old) psychiatric admissions and found that 26 percent of the moderate drug users, but only 5 percent of the extreme drug users, had a schizophrenic diagnosis.

These data indicate significant rates of drug usage among schizophrenic patients before their admission to treatment, but not necessarily at a rate exceeding that found among other diagnostic categories. While most of these studies acknowledge an apparent interaction between drug abuse and psychosis, none succeeded in clarifying the relationship between drug use and the onset of psychotic symptoms.

**Drug Abuse Among Hospitalized Psychiatric Patients**

Substance abuse is widespread among psychologically impaired individuals. Those psychotic patients who are also addicted to drugs present a unique challenge to treatment facilities, and many receive treatment for one or the other disorder, but rarely do both conditions receive specialized services (Pinson 1983).

While the rate of abuse among schizophrenic patients appears to be similar to that found among patients with other diagnoses, the specific drugs of choice have been shown to differ by diagnosis. The interaction of drug abuse and schizophrenia is poorly understood, although numerous authors have called for more research investigations of dual-diagnosis patients.

McLellan et al. (1978) found that nearly 60 percent of patients interviewed acknowledged use of alcohol, drugs, or both while in the hospital. Similarly, Alterman et al. (1980, 1981, 1982) found that a substantial number of patients had a history of drug abuse, and over half of them had used drugs while in the hospital. Alcohol abuse appeared to be more prevalent among hospitalized patients with a diagnosis of paranoid schizophrenia than among patients with other diagnoses.

Hasin et al. (1985) examined rates of alcohol and drug abuse among a large sample (n = 835) of inpatient subjects with affective disorders. Using relatively conservative ratings, they found nearly 23 percent of the subjects to have serious alcohol dependence problems, and 9 percent to have serious drug problems during their current affective
Substances Abused by Schizophrenic Patients

The co-occurrence of substance abuse and mental illness has been well documented, but relatively few authors have focused specifically on schizophrenic patients. Freed (1975) conducted a comprehensive review of the early literature on alcoholism and schizophrenia, and found few conclusive research findings despite the high co-occurrence of the two disorders. Among his findings was evidence that “alcoholism masks schizophrenia rather than vice versa” (p. 855), that alcohol abuse is more likely to follow the onset of schizophrenic symptoms than to precede them, and “a not insignificant proportion of schizophrenics are intemperate and... many alcoholics suffer an underlying schizophrenia” (p. 856).

Schneier and Siris (1987) provided a more recent review of drug abuse patterns among schizophrenic patients. They concluded that drug choices cited in 18 articles they reviewed were not random. Schizophrenic patients appeared to prefer stimulants and hallucinogens, and to use less alcohol and fewer sedative-hypnotics than did other psychiatric patients. The authors noted that the choice of stimulants is counter-intuitive since schizophrenic patients suffer from an agitated mental state. They speculated that if the schizophrenic patients were attempting to self-medicate their symptoms, hypnotics or sedatives would seem to have been more effective. The authors concluded that the potential benefits of stimulant use could be relief of negative symptoms, counteracting side effects of their neuroleptic medications, or both. They further speculated that the drugs of choice may be related to the subtype of schizophrenia or severity of symptoms, although no studies have directly addressed that possibility to date.

McLellan and Druley (1977) reported high rates of drug problems among schizophrenic patients (48 percent of paranoid patients and 43 percent of chronic patients), with alcohol being the drug of choice among 31 percent of the sample. Similarly, Alterman et al. (1980) reported that 50 percent of their schizophrenic sample who had a secondary alcoholism diagnosis continued to consume alcohol in the hospital.

In contrast, Rimmer and Jacobson (1977) encountered no greater rates of alcoholism among schizophrenic patients and their relatives than among the general population. Richard et al. (1985) also found relatively low rates of drug abuse (21 percent) in their sample. O’Farrell et al. (1983) examined addictive behaviors in hospitalized male veterans and found lower rates of alcohol abuse among schizophrenic patients than among all other psychiatric patients. Tsuang et al. (1982) compared substance abuse, along with other variables, among schizophrenic and nonschizophrenic patients and found more hallucinogen use but less sedative-hypnotic use in schizophrenic patients and no differences in the use of alcohol.

Although there is considerable disagreement about which drugs are most abused by schizophrenic patients, what emerges from these studies is confirmation that the co-occurrence of substance abuse and schizophrenia is widespread. Moreover, most authors recognized their inability to delineate the temporal relationship between the drug abuse and the onset of the psychotic symptoms. An understanding of that relationship is essential to determining the interaction of drug abuse and the onset of schizophrenia.

The Impact of Drugs on the Outcome of Schizophrenia

Some authors have examined the short-term impact of prior drug abuse on schizophrenic patients’ outcome by examining hospitalization records. Alterman et al. (1981, 1982) found drug-abusing hospitalized psychiatric patients (some of whom had schizophrenia) to have poorer attitudes toward treatment. Tsuang et al. (1982) examined the relationship of the duration of drug abuse (short vs. long) to length of hospitalization, length of pharmacotherapy, and discharge disposition and found those with shorter drug histories showed less pathology on all three measures. Miller and Tanenbaum (1989) examined several measures of hospital outcome (length of stay, time before first pass,
neuroleptic dosage, incidence of sign-out letters and medication refusals, seclusion imposition, and discharge status) for a small sample ($n = 55$) of male schizophrenic patients. Over one-half (55 percent) had abused drugs before admission. The only measure that was significantly different between the two groups was a higher rate of discharge against medical advice for the drug-abusing schizophrenic patients.

Other authors have conducted long-term followup studies documenting social-vocational adjustment and rehospitalizations of drug-abusing schizophrenic patients. McLellan et al. (1979) reported one of the few followup studies conducted on drug abusers. Their subjects ($n = 51$) were selected from a drug-abuse population on the basis of having 6 consecutive years of admissions to a Veterans Administration (VA) hospital after the index admission. The results revealed that although they all had low symptom levels when first admitted, over one-half of the stimulant users (6 of 11) subsequently developed psychosis and 5 were hospitalized for the disorder. The authors acknowledged that the subjects who chose stimulants may have had some prior subthreshold vulnerability, but the data did not allow confirmation or refutation of that possibility. This study illustrates the strength of prospective analyses and emphasizes the need to document the temporal pattern of the psychotic symptoms and the substance abuse, as well as, to the extent possible, the effect of premorbid personality.

In the followup study of drug abusers by Bowers (1977) cited earlier, he successfully recontacted 15 formerly hospitalized patients who suffered from psychotic reactions to illicit drug use. His findings indicated that of the patients who were assessed, approximately half did well and half did poorly. He also noted that the extent of premorbid drug involvement did not relate to outcome. Vardy and Kay (1983) also followed up their LSD-psychosis subjects and found similar rates of rehospitalization (52.4 percent) to those of the schizophrenic comparison group (47.6 percent).

Perkins et al. (1986) recontacted the previously hospitalized drug-abusing/psychotic patients who were originally studied by Tsuang et al. (1982) and found, after 10 years, that those who had more serious psychotic symptoms at their index hospitalization did more poorly than those who had drug reactions with psychotic features. Specifically, the more chronically psychotic former drug abusers were less likely to be employed and had more frequent hospital admissions than those with psychotic reactions of short duration. The gross measures of temporal interaction of substance abuse (long vs. short) and psychopathology in this study did not allow the investigators to perform a more detailed analysis of their interdependence.

McLellan et al. (1983) conducted a 6-month followup of alcoholics and drug addicts who had been enrolled in rehabilitation programs. Those patients who presented with more severe psychiatric impairment failed to improve, while those who were less impaired all showed considerable improvement.

Large scale followup studies on drug abusers are rare, and practically nonexistent among schizophrenic substance abusers. There is a clear need for an investigation involving comprehensive assessments of premorbid personality, family history of psychopathology, and drug use habits of schizophrenic subjects at the time of their admission. This cohort needs to be monitored in the hospital and then followed for several years.

**Future Directions in Research**

It is evident from the preceding review that substance abuse may profoundly affect the course and outcome of schizophrenia. It is also evident that many questions remain unanswered about (1) the precipitating role of drugs in the development of schizophrenia, (2) specific drug/schizophrenia dose-response interactions, and (3) the long-term prognosis for schizophrenic patients who also abuse drugs.

As several authors noted in the research discussed above, drugs can mimic or augment the psychotic symptoms found among psychiatric patients. This fact underscores the need to obtain differential diagnoses for all patients who present with psychotic features. Gold and Dackis (1986) advocate routine drug screens in all new patients, and especially in instances of psychosis of sudden onset. More involved assays of blood and urine are indicated when there is suspicion that specific substances are being abused. Ingram (1985) echoed the need for careful diagnosis, given the propensity of hallucinogenic drugs to mimic schizophrenia. As has been noted above, he asserted a need for careful premorbid personality assessment as well as a careful history of drug usage. Pinsker (1983) advocated the use of the schizophreniform diagnosis for all cases in which substance abuse is a contributing cause of the observed symptoms. He also indicated that treatment objectives need to be oriented to the primary diagnosis, be it schizophrenia or substance abuse.
Tsuang et al. (1982) emphasized the importance of the interaction of drug abuse on the course and outcome of schizophrenia as well as poorer premorbid personality than did drug abusers. Their evidence indicated a positive family history of psychosis and affective disorders as well as the age of onset of schizophrenic symptoms among the drug-abuse/schizophrenia group was significantly earlier than that of the schizophrenia only group. Despite similarities in the nature and number of symptoms exhibited by each group, these important findings need to be replicated with a larger sample and more careful documentation of early childhood development.

An additional factor of great importance is the determination of family history of psychopathology. Tsuang et al. (1982) emphasized the importance of careful assessment of premorbid personality as well as family history variables when diagnosing psychosis among drug abusers. Their evidence indicated that drug abusers with chronic psychotic symptoms were more likely to have a positive family history of psychosis and affective disorders as well as poorer premorbid personalities than did drug abusers with more acute psychoses.

Two research designs that might further our understanding of the impact of drug abuse on the course and outcome of schizophrenia are described below. The first approach is a large epidemiological analysis to ascertain prevalence rates of each disorder separately, as well as the rates of co-occurrence, paired with an assessment of psychiatric service utilization at several later intervals. The second design involves a prospective analysis with extensive history taking and longitudinal followup.

A Prevalence Study. A multistage strategy is needed, involving a large nationally representative initial sample of noninstitutionalized subjects who are old enough to have been exposed to the risk of developing substance dependence. The results of the Epidemiologic Catchment Area program (Robins et al. 1984), which used the Diagnostic Interview Schedule (DIS; Robins et al. 1985), provided reasonable estimates of prevalence. The lifetime prevalence rate for serious drug abuse was found to be approximately 11 percent in the 18- to 44-year age range, and nearly 2 percent for schizophrenia (Robins et al. 1984).

A survey package containing a self-administered diagnostic instrument such as the DIS, and a comprehensive drug use questionnaire such as the Youth Survey Questionnaire (YSQ; World Health Organization 1980) should be used to assess probable psychiatric disturbance. Relevant information on risk and protective factors needs to be obtained, as does specific differentiation of quantities and frequencies of abuse of various drug types. The YSQ contains three sections: demographic items, questions concerning the frequency and age of first use of 13 types of drugs, and two items assessing the honesty with which questions are answered.

The sample obtained from the initial mailing (stage 1) should be matched on age, sex, race, and socioeconomic status with an equally sized sample of nondrug users who are free of apparent psychopathology. All of those screened positive for drug abuse and dependence, and those screened positive for potential mental illness, as well as the sample of those screened negative for both disorders, should then be contacted by telephone in stage 2. The structured telephone interviews should use instruments such as the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al. 1986) to elicit relevant information to confirm a diagnosis of substance dependence and/or abuse. The rate of comorbidity within this sample is an empirical question.

Stage 3 of this study should involve recontacting the identified cohorts annually over a 5-year period to track subsequent drug abuse and psychiatric disturbances using similar instruments.

If we assume that a final sample of 3,000 drug abusers and 500 schizophrenic patients is needed to allow for attrition over the subsequent years of followup (stage 3), and if we further assume that only about 65 percent of those who are originally screened (stage 1) will be successfully contacted by telephone (stage 2), it will be necessary to have 10,000 individuals screened positive from the general mail survey (stage 1). If we also assume an 80-percent response rate to the first stage survey, and prevalence rates similar to those found by Robins et al. (1984), over 50,000 individuals will need to be canvassed in the initial stage of this study.

A Hospitalization Study. The primary issue to be considered in this design involves careful differential diagnosis of both the drug and
the psychotic condition. Other issues of concern include (1) the temporal relationship between drug use and the onset of schizophrenic symptoms, (2) the quantity and frequency of drug(s) consumed, (3) a careful assessment of the premorbid personality, and (4) the family history of somatic and psychiatric disabilities (including substance abuse). The final issue is the outcome of these subjects over time.

The complexity of this issue, resulting from the large number of drugs being abused and the great potential for interaction among dosage, frequency, and subsequent psychopathology, requires that a very large sample of affected individuals be obtained. Consequently, schizophrenic admissions will be needed from multiple psychiatric facilities around the country. It will be essential to obtain unambiguous differential diagnoses of both the presenting psychosis and the current drug involvement.

It can be anticipated that at least one-third of the admissions will have abused drugs at some time before their admission. If a final sample of 3,000 schizophrenic patients with a confirmed history of drug abuse is needed, and is to be matched with an equal sample of nondrug-abusing schizophrenic patients as a comparison group, approximately 10,000 admissions will need to be screened.

Several structured diagnostic interviews have been developed to aid in this process. For instance, Hasin and Grant (1987) have compared the relative effectiveness and reliability of the RDC with the Schedule of Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978) and the DIS. They found high reliability for substance abuse diagnoses, but less agreement on antisocial personality disorders. The SCID provides a highly reliable diagnostic confirmation and can be administered by trained lay interviewers.

The assessment of prior substance abuse behavior and the onset of personality deterioration would be greatly enhanced by the use of a collateral informant. The collateral could be a spouse, roommate, close friend, sibling, or parent. The temporal pattern of substance abuse and psychotic symptoms could be determined with modifications to the Time-Line Follow-Back Drinking Behavior Interview (Sobell et al. 1979). The Time-Line method anchors specified target behaviors to holidays, birthdays, and other significant life events, thereby greatly increasing the reliability of the subjects' recollections. Comparison of the subjects' recollections of events with those of the collaterals will also increase the accuracy of these reports.

An assessment of the extent of the history of both somatic and psychiatric disturbances among first- and second-degree relatives is also essential. Family history of alcoholism has been reliably recorded using the Family Tree Questionnaire for Assessing Family History of Drinking Problems (Mann et al. 1985). Once again, this instrument could be easily modified to capture broader medical histories for family members.

An essential element of this project would be to follow patients who screen positive for both schizophrenia and substance abuse, and compare their course of treatment and outcome with the nondrug-abusing schizophrenic comparison group. The large sample size would also make further analysis of treatment course and outcome possible by, in addition to the type of drug abused and the quantity and frequency of the abuse, family history and premorbid personality factors.

Conclusions

It is evident from the previous discussion that the impact of substance abuse on the course and outcome of schizophrenia remains largely undefined. There is some evidence that drugs tend to hasten the age of onset of psychosis, but it is unclear whether the effect is to precipitate latent or subliminal psychotic behavior or to initiate psychosis in subjects who would not have had an episode absent their drug abuse. Drug abuse just before hospitalization and during hospitalization is fairly common, and the drugs of choice do not appear to be random, but it has yet to be determined whether the specific benefits the schizophrenic patients are receiving from the drugs differ from those experienced by nonschizophrenic individuals. The relationship between characteristics of drug abuse (drug type, quantity and frequency of drug abuse) and the degree of psychopathology, manifestations of disease, and long-term outcome has yet to be addressed. Finally, drugs may be precipitating relapse and subsequent rehospitalizations among schizophrenic patients who are in remission.

The volume and complexity of the issues that remain unresolved must be addressed in a comprehensive and systematic manner. Two large-scale research efforts are outlined which could begin to provide some of the answers to these questions.
References


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