Considerations on "Organic" Exclusion Criteria for Schizophrenia

by John M. Kane and Jeffrey Selzer

Abstract

Given the variety of "organic" or "toxic" conditions that may produce, precipitate, or exacerbate psychotic disorders, it is important to attempt to clarify existing nosologies and to highlight the need for research strategies that may help to validate relevant distinctions. This review provides a brief discussion of some of those issues.

Numerous diseases and/or toxic states can affect brain function to such an extent as to produce transient or relatively persistent alterations in affect and cognition. These alterations may mimic those psychotic disorders that lack a currently known or detectable pathophysiological basis (Davison and Bagley 1969; Davison 1983).

To clarify existing nosological concepts and stimulate advances in our ability to validate relevant distinctions, numerous possibilities of cause and effect, interaction and outcome need to be organized into conceptual categories.

1. There is a group of diseases or toxic states that is capable of producing a psychotic state but whose pathophysiologies are relatively well understood. Examples include tertiary syphilis, Huntington's chorea, and hypoparathyroidism.

2. Other disorders may be found to have what appears to be a greater-than-chance association with psychotic states; however, the extent to which this implies a causal link remains far from established, given methodological problems and the paucity of studies that could help validate etiologic assumptions or hypotheses. Examples of such disorders include epilepsy and cerebral tumors.

3. There are factors that may not be sufficient to cause persistent psychoses but that may precipitate the condition in vulnerable individuals, or influence its age and/or mode of onset or its course and/or treatment response. Examples of such factors include substance abuse, some infectious diseases, or brain injury.

4. Certain organic factors appear to be concomitant features of psychotic disorders but are sequelae of the same underlying disease process. Examples include abnormal brain imaging findings, cognitive deficits such as memory dysfunction, some forms of abnormal involuntary movements, and neurological soft signs.

5. Some factors may be concomitants or consequences of the illness but ultimately may also have an impact on the course of the disease. An example would be the "self-medication" hypothesis of alcohol abuse or of particular stimulant or hallucinogenic abuse among individuals suffering from schizophrenia. Self-medication may be an attempt to influence the symptoms of the disease itself or to alleviate the subjective component of adverse effects associated with somatic treatment.

The challenge to current nosology is to be able to articulate these possibilities to clinicians even if we cannot provide precise criteria on which to base what ultimately become clinical judgments. The current DSM-III-R (American Psychiatric Association 1987) organic exclusion criteria: "...it cannot be established that an organic factor initiated and

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maintained the disturbance” (p. 195) provides little guidance to the clinician. The challenge is to avoid premature closure once a “diagnosis” is given and to foster further clinical attempts to gather potentially relevant or validating information.

Can nosology be improved beyond the addition of more frequent caveats or what become, in effect, exhortations to good clinical practice? This problem is frequently encountered today in attempts to differentiate between organic delusional syndrome or organic hallucinosis and schizophrenia. Most clinical observers agree that psychotic signs and symptoms can result from ingestion of hallucinogenic substances such as lysergic acid diethylamide (LSD) and phencyclidine (PCP), and that in some cases these reactions can persist for more than 48 hours. The critical distinction for our purposes relates to how these psychotic reactions can be distinguished from schizophrenia on a phenomenological basis and/or on the basis of course and outcome. An additional possibility is that associated features might be helpful in making a differential diagnosis.

Davison (1987) reviewed reports of complications that occurred following the administration of LSD. In a series of 25,000 administrations of LSD to 5,000 patients in the United States, a rate of “prolonged” (> 48 hours) psychosis was reported in 0.08 percent of experimental subjects and in 0.18 percent of patients receiving LSD for therapeutic purposes. In a review of clinical experience with LSD in Great Britain (Davison 1987), prolonged psychosis occurred at a rate of 0.9 percent with duration varying from less than 2 weeks to over 3 months. Persistent psychosis occurred in 10 patients. This rate of psychosis is certainly not greater than that in the general pop-

ulation, and it leaves unanswered the question of whether these were de novo psychotic states or psychotic reactions occurring in vulnerable individuals.

Most clinicians have based a differential diagnosis on the duration of the psychosis after ingestion of the toxic substance has ceased. The important issues become the validation of duration criteria and the degree of sensitivity and specificity that is acceptable. The problem is further complicated by the fact that psychotic reactions to hallucinogens that come to treatment and persist for more than a few days or a week are likely to be treated, which makes distinctions based on natural course particularly difficult.

Bowers (1987) has suggested that hallucinogen use can produce mental illness in vulnerable individuals and can precipitate relapse in those already affected. This conclusion is based on State hospital admission data showing an increase in admissions for schizophrenia and paranoid disorders occurring years after a peak in admissions for drug abuse. Clearly, there are numerous problems in drawing conclusions from these data. Grinspoon and Bakalar (1979, 1986) have emphasized the methodological problems in relating persistent psychoses to hallucinogen use, and they suggest that true psychotic experience associated with hallucinogen use usually lasts less than 48 hours.

There are strategies that could be brought to bear in validating assumptions regarding the problem—specifically, longitudinal followup, family studies, and investigations of associated features would be helpful. If longitudinal studies could examine patients experiencing prolonged psychotic episodes following hallucinogen use and show that the course of these psychoses differs from the course of those unassociated with substance abuse (assuming the cessation of substance abuse), this would be useful. If studies showed a difference in course, this would not necessarily clarify etiology but it would certainly be useful in planning treatment strategies.

If the “vulnerability” model is appropriate, those individuals with psychosis associated with hallucinogen use might have similar genetic loading to schizophrenic patients without a history of substance abuse. Again, the absence of similar genetic loading would not necessarily prove a causal relationship. Vardy and Kay (1983) conducted a study relevant to this issue. These investigators found that family history of schizophrenia was not different, but family history of substance abuse (specifically alcohol) was greater in the substance abuse group. Tsuang et al. (1982) reported that among drug abusers with psychoses of a longer duration they found more premorbid personality disorders and greater familial risk of schizophrenia and affective disorders as compared to those drug abusers whose symptoms lasted less than 6 months. But as Davison (1987) has pointed out, both studies have potentially serious methodological flaws. In the Tsuang et al. (1982) study, over half the cases in their prolonged drug psychosis group were apparently experiencing psychotic symptoms before their ingestion of drugs. In the Vardy and Kay (1983) study, the family data were obtained from case records, and age correction was not used in calculating the familial prevalence of schizophrenia. In addition, no concurrent control group was studied, but conclusions regarding the familial incidence of schizophrenia were based on comparisons with data in the literature. Hekimian
and Gershon (1968) reported that 50 percent of hallucinogen abusers admitted to hospital for psychotic symptomatology showed "signs" of schizophrenia before initial hallucinogen use.

Tsuang et al. (1982), Erard et al. (1980), and Breakey et al. (1974) have suggested that patients with drug abuse and psychoses appeared to experience an earlier age of onset of psychotic symptoms and/or earlier age of first hospitalization, but these differences are not consistently dramatic.

Dixon et al. (in press) compared drug-using and non-drug-using schizophrenic subjects and found a significantly greater family history of drug abuse in the former but no difference in family history of schizophrenia. Substance abusers demonstrated significantly lower rates of eye-tracking impairments than did non-substance-abusing patients. There were no differences on computed tomography measures of ventricular enlargement. There were also no differences on clinical measures of positive or negative symptoms at time of admission; however, drug users showed less severe symptoms (i.e., greater improvement) at time of discharge.

PCP has been associated with psychotic episodes and appears to have a higher abuse potential than LSD, mescaline, or psilocybin. Most observers seem to agree that PCP-induced psychoses remit within a day or two, but some cases have been described in which psychoses persisted for several weeks (Fauman and Fauman 1980; Grinspoon and Bakalar 1986). Luby and Cohen (1959) described a striking and persistent (for 1 month) exacerbation of psychosis in chronic schizophrenic patients receiving PCP.

There is a general consensus that psychotic signs and symptoms can be produced by cocaine and other central nervous system stimulants in "normal" individuals given high enough repeated doses (Angrist 1983; Kleber and Gawin 1986). Although anxiety symptoms are the most common, paranoid delusions and hallucinations can occur, but they usually remit within 48–72 hours (Resnick and Resnick 1984). Although Gawin and Ellinwood (1988) assert that stimulant-induced delusions can persist for weeks, no specific data or citations are provided. DSM-III-R also states that cocaine-induced delusions occasionally linger for over 1 year.

Angrist (1983) has reviewed the induction of psychotic symptoms among normals following oral d-amphetamine and intravenous methylamphetamine. Intravenous and oral methylphenidate have also been shown to be capable of producing psychosis resembling paranoid schizophrenia. The fact has been well established that some schizophrenic patients also experience a clear-cut psychotic exacerbation (though usually persisting less than 24 hours) following administration of amphetamine or methylphenidate under double-blind experimental conditions (Janowsky et al. 1973; Janowsky and Davis 1976; Angrist et al. 1980, 1985; Lieberman et al. 1984).

Numerous reports have suggested cannabis use to be associated with prolonged schizophrenia-like psychosis. As Davison (1987) emphasized, estimates of prevalence have varied widely. Davison (1987) cites data from a U.S. Army population of 36,000; researchers observed 720 cannabis smokers for 3 years. Among these individuals, 3 cases of persistent schizophrenic reaction occurred in smokers of 10–50 grams per month and 112 cases occurred in smokers of 25–200 grams per month, providing an overall incidence of 0.9 percent per year. However, it is important to note that many of these individuals were also abusing LSD, amphetamines, and alcohol.

Stefanis et al. (1976) reported a paranoid schizophrenia developing in 3 (6.4%) of 47 chronic cannabis users. Andreasen et al. (1987) reported that Swedish conscripts who were high users of cannabis had a relative risk of schizophrenia that was six times that of nonusers. The relative risk for schizophrenia was 2.4 times greater in the group that reported use of cannabis at least once compared with nonusers; the sixfold greater risk was found in those who had used cannabis more than 50 times. Occurrence of schizophrenia was not related to alcohol consumption. However, the variable that best predicted the development of schizophrenia at followup was "psychiatric diagnosis at conscription." Was cannabis a cause or an effect of psychosis? Interestingly, greater than 50 percent of the high cannabis users also had a "psychiatric diagnosis" at conscription. In another study focusing only on Stockholm County, 8,483 men who conscripted in 1969–70 for military service were investigated. A strong association was found between levels of cannabis consumption and treatment for schizophrenia. The relative risk for schizophrenia was 2.1 in the group that reported use of cannabis at least once compared with nonusers, and 4.1 among those who had used it more than 50 times (Andreasen et al. 1989). In contrast, Weller and Halikas (1985) found no increase in psychiatric diagnoses in 100 regular cannabis users at 6-year followup compared with a control group.
This review lends support to the possibilities outlined in the introduction regarding the various ways in which substance abuse may be associated with psychotic disorders. Basically, there is nothing particularly new or revealing in the recent additions to our knowledge base as they might affect nosology and differential diagnosis.

The difficulty with the current exclusion criteria is that they provide little guidance to the clinician as to what constitutes sufficient evidence that an organic factor initiated and maintained the disturbance. If we focus, for example, on the issue of substance abuse as an 'organic' factor, the following questions should be considered:

1. What constitutes sufficient evidence that a substance (and then a specific substance) has been ingested?
   a. History
   b. Toxicology
   c. Acute signs and symptoms of intoxications either by history or by observation

2. What constitutes sufficient evidence that there is a relationship between drug ingestion and subsequent psychopathology? What chronological proximity is necessary? The current term is 'shortly.'

3. Are there aspects of the phenomenology that would support a diagnosis of substance-induced organic mental disorders?

4. Are there differences in the course of signs and symptoms, both evolving and resolving, between these conditions—specifically and in general—as compared with schizophrenia or schizophreniform disorder?

5. Are there differences in associated features—for example, insomnia, appetite dysregulation, anxiety, etc.?  

6. Are there associated physiological (e.g., autonomic), neuropsychological (e.g., attention and information-processing), neurophysiological (e.g., smooth pursuit eye movement), or neurological (e.g., soft signs) features that might be useful?

7. If there is a period with return to normal cognition and behavior after acute intoxication and before reemergence of psychosis, does this constitute evidence that the psychosis is not drug-induced? If so, what duration of normal function would be sufficient?

8. What duration of psychosis following drug ingestion would argue against a drug-induced psychosis?
   a. Should this duration be based on the pharmacokinetic properties of the drug?
   b. Should it be based on data regarding the longest duration of a drug-induced psychosis with subsequent complete recovery?

9. What categories, if any, should be available to clinicians to identify possible or probable etiological factors in this context?

10. If substance abuse plays a role in 'precipitating' a psychosis that subsequently meets criteria for schizophreniform disorder or schizophrenia, does this factor have any implications for treatment (either short or long term), course, etc.?

11. Does long-term substance abuse have implications for course, treatment response, or phenomenology? Does this represent a meaningful subtype or is the 'dual diagnosis' the appropriate categorization?

Despite the frequency with which clinicians are called upon to make judgments in this context, it is striking how few empirical data are available from which to draw even the most tentative conclusions.

References


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