

DSM-*V* Research Agenda: Substance Abuse/Psychosis Comorbidity

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For diagnosis of patients with comorbid psychotic symptoms and substance use disorders (SUDs), *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, makes clear distinctions between independent psychotic disorders (eg, bipolar disorder, schizophrenia) and substance-induced syndromes (eg, delirium, dementias). Most substance-induced psychotic symptoms are considered to be short lived and to resolve with sustained abstinence along with other symptoms of substance intoxication and withdrawal. These guidelines are challenged by practical difficulties in distinguishing between substance-induced and independent psychoses and by mounting evidence that marijuana use may be a contributing cause of schizophrenia. To inform the diagnostic distinction between substance-induced vs independent psychotic symptoms, 2 kinds of information could be sought from longitudinal research: (a) identification of early markers that clearly differentiate the 2 conditions and (b) more precise information about duration of psychotic symptoms induced by different substances. Evidence of this type could emerge from reanalysis of existing data from large-scale longitudinal studies of community samples. To inform possible nosological changes related to the possible schizophrenia-inducing role of marijuana (eg, designating a “cannabis-induced” subtype), a wide range of research evidence will be needed to clarify the relationship between effects of cannabis and schizophrenia symptoms. Ultimately, the ideal psychiatric nomenclature will define syndromes on the basis of established etiology and/or pathophysiology. Given the strong association between SUDs and psychotic disorders, research on the neurobiology of psychotic disorders could fruitfully include subjects with comorbid SUDs to shed light on shared etiology and pathophysiology.

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One of the most common challenges for psychiatric diagnosis is posed by patients who experience the onset of psychotic symptoms during episodes of current or recent psychoactive substance use.¹ In *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*,² all major categories of nonorganic psychotic disorders include an exclusion criterion that “symptoms are not *due to* the direct physiological effects of a substance (e.g. p. 327, Major Depressive Episode, emphasis added).” In practice, determining whether a given psychotic symptom is “due to” drug effects is far from straightforward. In a study of first episodes of psychosis, Fennig and colleagues³ were unable to make a clear diagnosis in 25/278 cases, and substance abuse was the most common cause of diagnostic ambiguity. Shaner and colleagues⁴ characterized the sources of diagnostic confusion in a study of 165 patients with chronic psychosis and substance abuse on whom a “definitive diagnosis” could not be arrived at. Most common factors clouding diagnosis were identified as insufficient abstinence (78%), poor memory (24%), and inconsistent reporting (20%). While current substance abuse in psychotic patients poses practical challenges for the diagnostic *process*, do these diagnostic dilemmas point to the need for changes in the *DSM-IV* diagnostic *criteria*? In this article, I will review *DSM-IV* guidelines for diagnosing comorbid psychotic disorders and substance use disorders (SUDs), the factors undermining definitive diagnosis of comorbid disorders, potential nosological changes that could address these issues, and the types of research that could inform a revision of criteria and guidelines for diagnosing comorbid SUDs and psychosis.

DSM-*IV* Guidelines for Diagnosing Comorbid Psychotic Disorders and SUDs

In keeping with the atheoretical and phenomenological principles of St Louis psychiatry,^{5,6} *DSM-IV* encourages listing all diagnoses, past and present, for which a patient meets criteria. For patients with SUDs, psychotic disorders can be diagnosed as “independent” or subsumed under one of the many “substance-induced” mental disorders of which psychosis is a feature. With variations

related to the pharmacological effects of different categories of substances (eg, alcohol, opioids, stimulants), these include acute intoxication, intoxication delirium, withdrawal, alcohol-induced persistent dementia, and substance-induced psychotic disorder with hallucinations. Because “independent” psychotic diagnoses (eg, schizophrenia, bipolar I) are not to be made if symptoms are due to effects of substances, newly emerging psychotic symptoms in the presence of substance abuse (or withdrawal) are presumed to be “substance induced” until proven otherwise. In psychotic patients who use substances, evidence for “independence” of psychotic symptoms requires onset of symptoms during a drug-free period or persistence of psychotic symptoms during a period of sustained abstinence from psychoactive substances (when intoxication or withdrawal effects can no longer account for psychotic symptoms). Except for alcohol-induced pathological dementia, all the substance-induced psychotic mental disorders are considered to be time limited.

Difficulties in Applying *DSM-IV* Guidelines for Diagnosing Comorbid SUDs and Psychotic Disorders

Disentangling the relationship between SUDs and psychotic disorders is a commonplace diagnostic challenge for both clinicians in treatment settings and researchers in community settings. US community surveys, such as the Epidemiology Catchment Area and National Comorbidity Survey, document an association of most classes of mental disorders with SUDs, with a particularly high association between bipolar disorder and SUDs.^{7,8} Clinical samples of patients with schizophrenia and bipolar disorder report even higher rates of SUDs, suggesting that comorbidity contributes to treatment seeking.^{9–12} In fact, for patients with both comorbid SUDs and schizophrenia, rehospitalization is frequently associated with relapse to drug use along with discontinuation of prescribed antipsychotic medications.^{10,12}

When patients present with current or recent substance abuse and psychosis, the key diagnostic question is whether or not the psychotic symptoms are accounted for by the substance use. If so, then antipsychotic treatment can be seen as short term while central emphasis is placed on substance abuse treatment. If not, then major emphasis must be placed on long-term care of the independent psychotic disorder, as these disorders tend to be chronic and associated with severe and sustained psychosocial impairment.¹ Psychotic syndromes can be considered as “independent” of substance use if they have an age of onset prior to the onset of SUDs or if psychotic and other symptoms persist during sustained drug-free periods. Another central differential diagnostic feature of “independent” psychotic disorders is that they are characterized by having a clear sensorium, as disorientation is a key feature of the delirium that is associated with many substance-induced psychotic syndromes. In prac-

tice, several features of comorbid SUDs and psychosis cloud the picture. First, patients may report no sustained drug-free periods. Both SUDs and psychotic disorders are chronic conditions that most typically begin during teen years or young adulthood. Once a pattern of sustained drug abuse begins, sustained periods of abstinence may be absent or infrequent. If psychotic symptoms emerge during periods of heavy drug use, these may indeed be “substance induced,” but they may also be manifestations of an independent illness that happens to be emerging at the same time or that may be precipitated by the concurrent substance use. Second, it is difficult to establish or practice precise guidelines for specifying the amount of time that defines a “sustained drug-free period.” For hospitalized or closely supervised patients, treatment may lead to detoxification from substances, but lengthy inpatient stays are now the exception and not the rule. Moreover, substance-induced psychotic symptoms may persist long after cessation of use. For example, a recent review of studies of stimulant-induced psychoses noted that 1%–15% of patients had psychotic symptoms that persisted greater than 1 month.¹³ Further complications arise for patients who abuse multiple substances, each of which with a differing profile of psychotogenic effects and duration of withdrawal syndromes. Third, patients with comorbid psychotic disorders and substance abuse are likely to have a poor memory of the precise sequence of events that occurred during their teens, such as pinpointing the onset of initial psychotic symptoms vs the initiation of heavy substance use. Fourth, establishment of a “clear sensorium” is difficult even in acutely psychotic patients who do not use substances because of cognitive deficits, confusion, and difficulty in cooperating with the examiner. Fifth, the profile of psychotic symptoms associated with heavy substance use (particularly of stimulants) is difficult to distinguish from independent psychotic disorders. For example, a recent review of stimulant-induced psychosis¹³ documented the following rates of reported symptoms: paranoia (25%–75%), auditory hallucinations (50%–80%), ideas of references (15%–60%), Schneiderian first-rank symptoms (up to 50%), and negative symptoms (5%–30%).

Emerging Findings on Substance-Induced Psychotic Disorders

In addition to the everyday practical challenges to differentiating “substance-induced” from “independent” psychotic disorders, a major issue related to the etiology of psychotic disorders is whether or not psychoactive substance use can be considered a “cause” of schizophrenia, a condition that has been traditionally thought of as “independent” of substance use. Recent interest has focused on the relationship of teen and young adult cannabis use to increased risk for a subsequent diagnosis of schizophrenia. In a meta-analytic review of 7 longitudinal

studies, Henquet and colleagues¹⁴ report a 2.1 odds ratio for increased risk for schizophrenia in cannabis users. Intriguing clues for a possible genetic basis for this increased use have been reported by Caspi and colleagues¹⁵ who documented a stronger association between cannabis use and schizophrenia for subjects with the Val-Val variant of the *COMT* gene. From a nosological standpoint, research of this type raises important questions about the definition of the schizophrenia syndrome itself. Are episodes of “schizophrenia” that are induced by cannabis use identical with those that are not? If not, then some type of designation of a subgroup of schizophrenia would be useful for denoting this substance-induced variant. Alternatively, if the cannabis-induced syndromes are identical to independent syndromes, this suggests the value of studying cannabis effects to identify neurobiological processes underlying schizophrenia. As noted above, aside from alcohol-induced dementia, substance-induced psychoses have traditionally been considered to be time limited and the role of drugs in causing more enduring psychoses has been that of precipitating or facilitating expression of an underlying psychotic process.

How Can *DSM-V* Address Diagnostic Challenges and Emerging Findings?

In considering the potential nosological impact of emerging findings about substance-induced psychotic disorder or difficulties in distinguishing “substance-induced” from “independent” psychoses, it is important to recall that clinical challenges in diagnosis or new etiological findings have no straightforward relationship to amending the diagnostic system, itself. The difficulties in distinguishing substance-induced from independent psychotic symptoms are hardly new and were well known to framers of *DSM-III*, *DSM-III-R*, and *DSM-IV* criteria. The current guidelines embody the thinking of previous workgroups on the optimal way of handling these issues. Likewise, the impact of drug use on etiology of schizophrenia is one of many factors contributing to the disorder, and the general policy of the *DSM* and *ICD* (*International Classification of Diseases*) systems is to base diagnostic groupings on phenomenology of disorders and not on causes, given the lack of definitive knowledge about causes of any of the major mental disorders.¹⁶

If changes are to be made in *DSM-IV* related to comorbid psychotic disorders and SUDs, these can take place at several different levels including (a) rearrangement of groups of disorders (eg, subsuming SUDs, eating disorders, and impulse control disorders under a general category of “Addictions” or “Impulse Control Disorders”), (b) adding or deleting a diagnostic category, (c) changing diagnostic criteria, or (d) changing textual guidelines for determining the presence or absence of criteria. Response to the problems of differentiating substance-induced vs independent disorders would most likely be in the text

or in the criteria for specific substance-induced syndromes. Changes made on the basis of emerging findings about enduring psychoses caused by drug abuse could be at the syndrome level (eg, adding a “cannabis-induced enduring psychosis” diagnosis) or in the text describing characteristics of disorders.

To inform the diagnostic decision between substance-induced and independent psychotic symptoms, 2 kinds of information would be useful: (a) identification of early markers that clearly differentiate the 2 conditions and (b) more precise information about the duration of substance-induced psychotic symptoms. At present, the most definitive method for making this distinction is longitudinal assessment after a period of sustained abstinence from psychoactive substances. This is time consuming and often impractical given the relapsing nature of substance abuse and limited access to inpatient care. First, more rapid diagnosis could be facilitated by the identification of “markers” or distinctive clinical features that would identify patients with psychotic symptoms as having transient, substance-induced syndromes or enduring independent disorders. Such markers might take the form of biological indices (eg, a genetic profile suggesting schizophrenia), symptom profiles, or features of the psychiatric history. Recent works by Caton and colleagues¹⁷ and C. L. M. Caton, D. S. Hasin, P. E. Shrout, R. E. Drake, B. Bominguez, S. Samet, B. Shanzer (unpublished data) illustrate this approach. In a sample of 319 treatment-entering patients with psychosis and SUDs, reevaluation at 1-year follow-up revealed that 25% of psychotic diagnoses that had originally been designated as substance-induced were reclassified as independent. At initial evaluation, the reclassified patients differed from those with transient psychoses by being more likely to report parental mental illness, having poorer premorbid adjustment, and having less insight into their psychosis. Second, more definitive information could be gathered on the duration of substance-induced psychotic symptoms and syndromes. Numerous studies have evaluated characteristics and course of stimulant-induced psychosis,^{13,18–21} but less is known about the time course of transient psychotic syndromes resulting from use of other classes of drugs or from polysubstance abuse. At present, for purposes of differential diagnosis, “sustained” remission is considered to be around 4 weeks of abstinence. Conceivably, this duration of abstinence may be too short for psychoses induced by some substances (eg, cannabis or hallucinogens) or too long for those induced by others (eg, benzodiazepines).

Recent evidence suggesting that cannabis use may contribute as a cause of “schizophrenia” diagnosis¹⁴ could have an important impact on the understanding of psychotic illnesses and on the system for classifying these illnesses. From a practical, clinical standpoint, intervening with teenage marijuana use could prevent the development of a full psychotic syndrome in susceptible individuals. Such a preventive substance abuse intervention could

be coupled with early antipsychotic pharmacotherapy to intervene in the “prodromal” period of schizophrenia or other psychotic conditions.²² For understanding etiology, research on mechanisms of cannabis effects may point to neurobiological pathways underlying vulnerability to schizophrenia. Nosological changes that might be made on the basis of these findings would require considerably more evidence than is currently available. For example, enduring psychotic syndromes associated with prior cannabis use may constitute disorders that are distinctly different from what is now called “schizophrenia” and that would warrant classification as separate disorders. Delineation of such a syndrome (or syndromes) would require a considerable body of work documenting diagnostic distinctiveness, course, symptom features, and other types of evidence articulated by Robins and Guze⁵ for defining psychiatric disorders. Alternatively, the concept of schizophrenia that is “caused” by cannabis use suggests the possibility of designating subtypes of psychotic disorders on the basis of differing etiological factors, which could include genetic, developmental, or other causes.

Adding Substance Use to the Research Agenda on Nosology of Psychosis

Heterogeneity within categories of psychotic disorders (eg, schizophrenia) and lack of clear boundaries between major subtypes (eg, mood-related psychoses and schizophrenia) are major challenges for current official nomenclatures for psychotic disorders. These 2 general problems run through most of the papers in this series.²³ An additional challenge for defining homogenous, distinctive subtypes based on etiology and pathophysiology is posed by highly prevalent comorbid abuse and dependence on psychoactive substances that can cause at least temporary psychotic symptoms. For example, use of stimulants by schizophrenic patients may cause euphoria after initial use followed by a dysphoric “crash” that may mimic bipolar disorder.⁹ Alternatively, use of stimulants by schizophrenic patients may, in itself, be an indicator of manic disinhibition and point to a diagnosis of schizoaffective disorder.

An improved diagnostic system for comorbid psychotic disorders and SUDs must arise from a better understanding of the relationship between these 2 broad classes of disorders. Research to clarify these relationships could be most efficiently conducted by 2 general strategies: (a) reanalysis of longitudinal surveys that include diagnoses of SUDs and psychotic disorder and (b) including patients with comorbid disorders in studies of the neurobiology and/or treatment of psychotic disorders.

As a first general strategy, important clues about the relationship between SUDs and psychoses can be gained through reanalysis of existing longitudinal data sets of community and clinical samples. Robins²⁴ has recently advocated this approach for addressing nomenclature

issues generally and identifies several major studies with longitudinal components including the Epidemiology Catchment Area Study,²⁵ the National Comorbidity Survey,²⁶ and the Detroit studies of Breslau and colleagues.²⁷ A more comprehensive review of public access data from community surveys of SUDs is provided by Cottler and Grant.²⁸ Issues that could be addressed in these analyses include the relationship of SUDs diagnosed in early waves to the onset of new psychotic disorders diagnosed at later waves or the relationship of SUDs to diagnostic instability of psychotic disorders across waves. For example, secondary analysis of data from existing longitudinal studies was the approach used for many of the reports on cannabis and increased risk for schizophrenic disorders reviewed by Henquet et al.¹⁴

A second general strategy to improve understanding of the SUD/psychosis relationship would be to include subjects with comorbid disorders in the full range of research projects for which the goal is to elucidate the etiology, pathophysiology, and treatment of psychotic disorders. Despite the high rates of psychoactive substance use in clinical populations of psychotic patients, research on the treatment and neurobiology of psychotic disorders tends to avoid potential confounds by excluding psychotic subjects with current substance abuse. Excluding substance-abusing patients from, for example, neuroimaging studies of bipolar patients has considerable merit for eliminating drug effects that might be mistakenly attributed to the bipolar disorder itself. However, findings from such research may not be generalized to bipolar patients who abuse substances and whose conditions could represent a distinct diagnostic subtype. In addition to scientific barriers to study of psychotic patients with comorbid SUDs, the organization of US National Institutes of Health research support creates another barrier to this type of research. Most research on psychoses is supported by the National Institute of Mental Health while research on SUDs is supported by separate institutes (ie, the National Institute on Drug Abuse and the National Institute on Alcoholism and Alcohol Abuse). While conjoint support across institutes is a possibility, such an arrangement is not the norm.

A third general strategy to elucidate the relationship between SUDs and psychotic disorders would be to initiate descriptive phenomenological studies that capture the onset of SUDs and nonorganic psychotic disorders. Informative samples for this research could include high risk, psychotic family history, positive teens and young adults who exhibit prodromal psychotic symptoms,²² or patients seeking treatment for a first episode of psychosis.³

DSM-V and Beyond

In reviewing literature on comorbid psychosis and SUDs coming out after publication of *DSM-IV*, I was unable to locate published criticism of those aspects of the official

nomenclature that specifically address the intersection between psychotic disorders and SUDs. This relative absence of discontent strongly contrasts with criticisms embodied in other papers in this series²³ pointing out the lack of clear boundaries between psychotic diagnoses related to mood disorders vs nonaffective psychoses, the unacceptably large heterogeneity within diagnostic subgroups, and the limitations of a categorical approach to the diagnosis of psychotic disorders. Ultimately, the ideal psychiatric nomenclature will define syndromes on the basis of established etiology and/or pathophysiology. For patients with comorbid psychosis and SUDs, this association may be explained by chance, shared common etiological factors for the 2 disorders, substance use contributing to the etiology of psychosis, or psychosis contributing to the etiology of SUDs. At present, except for the relatively narrow and transient group of “substance-induced” psychoses, the current diagnostic system is silent about hierarchical or causal relationships between disorders when patients qualify for multiple diagnoses. With emerging advances in knowledge about the shared etiology and neurobiology of SUDs and psychoses, these relationships may be reflected in a more advanced nomenclature. Looking toward *DSM-V*, no emerging findings related to either type of disorder can be said to justify major changes in the ways that psychosis/SUD comorbidity is currently diagnosed. In the absence of compelling need and a strong empirical basis for change, diagnostic conservatism is called for. It is important to remember the many costs of enacting major changes in nosology and to set a relatively high threshold for revision. These costs include the burden on clinicians, who must learn a new system; disruptions in research, particularly in longitudinal studies and in the ability to compare past and future studies; apparent changes in prevalence rates, which mainly reflect artifacts of syndrome definitions; the need to modify existing instruments or develop new instruments; and a negative public perception of vacillation or uncertainty.^{6,29}

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