Substance-Induced Psychosis: A Diagnostic Conundrum

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Objective: To critically examine the DSM-IV-TR criteria for substance-induced psychotic disorder (SIPD).

Data Sources: Leading electronic databases (such as MEDLINE, PubMed) were searched for the years 1992 through 2007, using combinations of the following key search terms: *substance abuse/dependence*, *alcohol*, *marijuana*, *cannabis*, *methamphetamine*, *crack*, *cocaine*, *amphetamine*, *ecstasy*, *ketamine*, *phencyclidine*, *LSD*, *mental health*, *drug-induced psychosis*, *substance-induced psychosis*, *psychosis*, and *schizophrenia*. References identified from bibliographies of pertinent articles and books in the field were also collected and reviewed.

Data Extraction: Only research studies or case reports/series that presented data on populations diagnosed with SIPD by using clinical or structured diagnostic interviews and that were published in English were used to assess the validity of the current SIPD criteria.

Data Synthesis: We identified 49 articles that presented clinical data on SIPD. Almost half of these publications were case reports, with 18 articles specifically focusing on delineating the clinical characteristics or outcomes of individuals diagnosed with SIPD. While several large studies have recently been conducted to assess the stability of SIPD, there is a dearth of research that rigorously examines the validity of DSM-IV diagnostic criteria across substances.

Conclusions: There remains a striking paucity of information on the outcome, treatment, and best practice for substance-associated psychotic episodes. Further work is clearly required before the advent of DSM-V. We propose an alternative, broader classification that better reflects the current evidence base, inferring association rather than causation.

(J Clin Psychiatry 2008;69:358–367)

Received March 5, 2007; accepted July 25, 2007. From the Department of Psychiatry, ORYGEN Research Center, University of Melbourne, Melbourne, Australia.

The authors would like to acknowledge the support of the Colonial Foundation, Melbourne, Australia. Dr. Mathias was supported by a fellowship from the University of British Columbia, Department of Psychiatry, Vancouver, British Columbia, Canada.

The authors report no additional financial or other relationships relevant to the subject of this article.

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The relationship between substance use and psychosis remains a contentious issue and is regularly debated within academic, clinical, and political circles. The debate has been particularly prominent of late, with the publication of a number of large cohort studies documenting a link between adolescent cannabis use and the development of psychosis in early adulthood.[1–3] Recent concern regarding the escalating use of methamphetamine worldwide and its association with psychotic symptomatology among regular users has also fuelled the debate.[4–6]

Within clinical practice, the issue is further complicated by high rates of co-occurring substance use disorders (SUDs) among individuals with a psychotic illness. Indeed, up to 50% of individuals with a history of schizophrenia report a coexisting SUD,[7,8] while rates among young people in the early stages of psychosis are even higher.[9,10] This level of comorbidity highlights the difficult diagnostic challenge faced by clinicians and researchers in accurately differentiating substance-induced psychotic episodes from primary psychotic disorders in the context of co-occurring substance misuse. There is, therefore, a clear need for a diagnostic framework that provides accurate, unambiguous, evidence-based clinical criteria.

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) was the last major revision of the DSM and resulted in significant, well-documented changes from the DSM-III-R.[11] Substance-induced psychotic disorder (SIPD) was created based on recommendations from the Substance Use Disorders Work Group, formed in 1988 to examine the issue of substance-induced states.[11] The SIPD criteria (Table 1) were constructed to detail specific timeframes and conditions aimed at distinguishing substance-induced psychotic states from primary psychotic disorders.

At the time of writing the original SIPD criteria, the most prevalent psychotogenic drugs used by young people were the stimulants cocaine and amphetamine, the hallucinogens lysergic acid diethylamide (LSD) and cannabis, and the more rarely used phencyclidine and mescaline.[12] While many of these drugs remain in common use today, young people also experiment with newer, more potent formulations.[12–14] For example, ecstasy and methamphetamine use among young people only began to escalate during the mid- to late 1980s (with crystal methamphetamine only increasing in prevalence

Table 1. DSM-IV-TR Criteria for Substance-Induced Psychotic Disorder[a]

A. Prominent hallucinations or delusions. Note: Do not include hallucinations if the person has insight that they are substance-induced.
B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):
   (1) The symptoms in Criterion A developed during, or within a month of, Substance Intoxication or Withdrawal
   (2) Medication use is etiologically related to the disturbance
C. The disturbance is not better accounted for by a Psychotic Disorder that is not substance-induced. Evidence that the symptoms are better accounted for by a Psychotic Disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non–substance-induced Psychotic Disorder (e.g., a history of recurrent non–substance-related episodes).
D. The disturbance does not occur exclusively during the course of delirium.

[a]Reprinted with permission from the American Psychiatric Association.[26]

relatively recently), and evidence regarding their association with psychosis was limited during the preparation for DSM-IV.[6,15–17] Similarly, little data were available regarding "crack" prior to 1985, although this potent crystalline form of cocaine has been associated with elevated rates of psychosis following heavy use.[18] Cannabis use among young people has also increased considerably since the 1980s, while the age at first use has dramatically decreased.[19,20] In addition, there is some evidence that cannabis is now used in a more potent form than in previous decades.[21,22] However, despite these changes in drug use trends, SIPD criteria have been applied by clinicians and researchers categorically since 1994, with no provisions within DSM-IV for what substances were considered in their development.

Further, when the SIPD criteria were first constructed, limited data were available regarding the high rates of substance use among individuals with psychotic disorders. While alcohol and tobacco remain the most frequently abused substances by individuals with psychotic disorders, the high incidence of cannabis, stimulant, and polysubstance use invariably complicates the diagnostic picture.[7,23–25]

The DSM-IV-TR,[26] published in May 2000, made limited changes as it "reflected the literature up to 1992." Only narratives and diagnostic codes were revised to more accurately reflect the *International Classification of Diseases, Ninth Revision, Clinical Modification*.[26] By the time DSM-V is published, nearly 20 years will have elapsed between the time SIPD was created and first revised. Given that the work groups for DSM-V have just commenced, a critical deconstruction of the SIPD criteria, as written in the DSM-IV, is clearly timely.

Aims of the Study

The primary aim of the current article was to critically examine each of the SIPD criteria (with the exception of criterion D) by using available data from the clinical research literature since 1992 (the cutoff year for research literature reflected in DSM-IV). A secondary aim, based upon these initial findings, was to propose a number of revisions to the criteria that reflect current clinical experience.

DATA SOURCES

Leading electronic databases (such as MEDLINE, PubMed) were searched for the years 1992 through 2007, with combinations of the following key search terms: *substance abuse/dependence*, *alcohol*, *marijuana*, *cannabis*, *methamphetamine*, *crack*, *cocaine*, *amphetamine*, *ecstasy*, *ketamine*, *phencyclidine*, *LSD*, *mental health*, *drug-induced psychosis*, *substance-induced psychosis*, *psychosis*, and *schizophrenia*. References identified from bibliographies of pertinent articles and books in the field were also collected and reviewed.

DATA EXTRACTION

Only research studies or case reports/series published in English that used clinical or structured diagnostic interviews to present data on populations diagnosed with SIPD were assessed. Epidemiologic studies reporting psychotic symptoms among populations of drug users or substance use among individuals with psychosis were not included if a diagnosis of SIPD was not formally assessed. Studies that primarily focused on genetic or neurobiological investigations were also excluded if they did not include a clinical description of the population.

DATA SYNTHESIS

We identified 49 articles that presented clinical data on SIPD. Approximately half (N = 24) were case reports describing SIPD in the context of cannabis,[27] prescribed dexamphetamine,[28] ecstasy,[29,30] methamphetamine,[31] khat,[32,33] LSD,[34] or psychotomimetic herbal use.[35–38] We identified 18 articles that specifically focused on delineating the clinical characteristics or outcomes of individuals diagnosed with SIPD (Table 2).

Criterion A

The diagnosis of psychosis associated with substance use is differentiated from the primary psychotic disorders by its narrower definition.[26] Criterion A defines SIPD by the prominence of 1 of 2 positive symptoms (hallucinations or delusions), although the term *prominent* is not clearly defined (in terms of either severity or duration of symptoms), which makes it difficult to apply in practice.

Table 2. Studies Examining the Clinical Characteristics or Outcomes of Individuals Diagnosed With SIPD

Study	Substance	Study Sample	Follow-Up	Findings
Caton et al[39] 2007 USA	Alcohol or drugs	N = 386 Substance users with DSM-IV SIPD or PPD using PRISM Recruited from psychiatric emergency departments	1 year	(1) 25% of SIPD patients had PPD at follow-up (2) PPD group characterized by poorer premorbid function, less insight into psychosis, and greater family mental illness than SIPD group (3) Diagnosis of substance misuse/dependence, lower PANSS score, and visual hallucinations predicted diagnostic distinction
Schanzer et al[40] 2006 USA	Alcohol or drugs	N = 302 Patients with early-phase psychosis with substance use Recruited from psychiatric emergency departments	1 year	(1) Of 223 patients diagnosed with PPD, 25% were determined to have SIPD or no psychosis (2) PPD patients were more likely than SIPD patients to be hospitalized, started on antipsychotics, and referred to psychiatry (3) Those found by the BELD[a] to have SIPD or no psychosis were more likely to be treated for PPD
Caton et al[41] 2006 USA	Alcohol or drugs	N = 319 Patients with early-phase psychosis with substance use and DSM-IV SIPD or PPD using PRISM Recruited from psychiatric emergency departments	1 year	(1) 1-year remission rates were 50% for PPD and 77% for SIPD (2) Predictors of remission for both diagnostic groups included lower baseline PANSS scores, better premorbid function, greater insight into psychosis, and shorter duration of psychosis
Akiyama[42] 2006 Japan	Methamphetamine	N = 32 Females with MIPD Recruited from incarceration site	Lesser of discharge from facility or 120 weeks	(1) 3 groups were differentiated based on relative (low, moderate, high) magnitude of symptoms, with differential treatment responses (2) 5 months were required to ameliorate symptoms even in the low-rating group
Leelahanaj et al[43] 2005 Thailand	Amphetamine	N = 58 DSM-IV AIPD subjects with BPRS score > 35	4 weeks	(1) 93% of olanzapine subjects and 79% of haloperidol subjects were improved at 4 weeks (2) Olanzapine was superior to haloperidol in treatment safety and severity of extrapyramidal symptoms
Caton et al[44] 2005 USA	Alcohol or drugs	N = 400 Patients with at least 1 psychotic symptom and alcohol or drug use in past 30 days and diagnosed with SIPD or PPD using PRISM Recruited from psychiatric emergency department	Baseline data of 3-year study	(1) 44% diagnosed with SIPD and 56% with PPD (2) 3 predictors of SIPD: parental substance abuse, diagnosis of dependence on any drug, and visual hallucinations (3) Total positive and negative symptom score was greater in PPD group
Arendt et al[45] 2005 Denmark	Cannabis	N = 535 Patients with ICD-10 CIPD Recruited from psychiatric hospitals	3 years	(1) Schizophrenia-spectrum disorders were diagnosed in 44.5% of sample; new psychotic episodes of any type were diagnosed in 77% (2) Sample group developed schizophrenia at an earlier age than non-CIPD comparison group
Batki and Harris[46] 2004 USA	Methamphetamine or cocaine	N = 19 Subjects with DSM-IV MIPD or CoIPD using SCID; Recruited from psychiatric emergency service		Methamphetamine or amphetamine plasma and urine levels correlated with several psychopathology scores and global hyperkinesia rating
Srisurapanont et al[47] 2003 Thailand Australia Philippines Japan	Methamphetamine	N = 168 Patients with methamphetamine use and evidence of SIPD using MINI-Plus[b] Recruited from inpatient setting		(1) 2-factor model of MIPD symptoms: positive/disorganized syndrome and negative syndrome (2) Most common lifetime psychotic symptom was persecutory delusions (77%) and most common current symptom was auditory hallucinations (3) Current negative symptoms found in 21% of patients
Chen et al[48] 2003 Taiwan	Methamphetamine	N = 445 Subjects with methamphetamine use; assessed with DSM-IV Recruited from psychiatric hospital or detention center		Those with MIPD compared with those without MIPD were younger at first use, used larger amounts, had higher mean PSST scores, and had higher rates of major depressive disorder, alcohol dependence, and personality disorder

(continued)

Table 2 (continued). Studies Examining the Clinical Characteristics or Outcomes of Individuals Diagnosed With SIPD

Study	Substance	Study Sample	Follow-Up	Findings
Nunez and Gurpegui[49] 2002 Spain	Cannabis	N = 25 Subjects with DSM-III-R CIPD compared with acute schizophrenia group Recruited from community mental health services		(1) Those with CIPD were more likely to be male and to have expansive mood or ideation, derealization/depersonalization, visual hallucinations, and disturbances in sensorium (2) Premorbid schizoid traits were more frequently associated with acute schizophrenia, antisocial personality traits with CIPD
Landabaso et al[15] 2002 Spain	Ecstasy (MDMA)	N = 32 Subjects with DSM-IV EIPD Recruited from drug abuse treatment centers	6 months	(1) Baseline mean BPRS score was 33.1 (severe), with severity falling by 49.5%, 71.1%, and 84.9% at 1, 3, and 6 months, respectively (2) Baseline mean HAM-D score was 22.0, with severity falling by 45.6%, 70.6%, and 85.3% at 1, 3, and 6 months, respectively (3) Baseline mean CGI score was 3.9
Harris and Batki[50] 2000 USA	Amphetamine or cocaine	N = 19 Subjects with DSM-IV AIPD or CoIPD Recruited from psychiatric emergency services		(1) All had preponderance of positive symptoms on PANSS (2) 26% had substantial negative scale scores, 95% had bizarre delusions, and 63% had Schneiderian hallucinations (3) Positive scores correlated to seclusion hours, negative scores to neuroleptic dose
Berk et al[51] 1999 South Africa	Cannabis	N = 30 Subjects with DSM-IV CIPD using MINI[b] Recruited from inpatient unit	4 weeks	(1) No difference on primary outcome measures (BPRS, CGI-Severity of Illness scale, CGI-Improvement scale) (2) Haloperidol group developed more extrapyramidal symptoms on Simpson-Angus Scale
Hernandez-Avila et al[52] 1998 Mexico	Inhalants	N = 40 Males with DSM-III-R inhalant dependence or inhalant-induced organic mental disorder Recruited from acute psychiatric unit	5 weeks	(1) Both treatment groups improved significantly; approximately half in each group were treatment responders (2) Adverse effects were significantly more common in haloperidol group
Rosenthal and Miner[53] 1997 USA	Psychoactive substances (no methamphetamine)	N = 65 Patients with DSM-III-R organic delusional disorder, organic hallucinosis, or both matched with schizophrenia sample Recruited from substance abuse inpatient unit	Time of admission to time of discharge	(1) Formal thought disorder and bizarre delusions predict schizophrenia (2) Suicidal ideation, intravenous cocaine abuse, and detoxification history or methadone maintenance inversely predict schizophrenia
Rosse et al[54] 1994 USA	Cocaine, PCP	N = 34 Subjects with DSM-III-R cocaine dependence using SCID compared with 16 chronic schizophrenic patients and 16 cocaine-dependent men with PCP use history Recruited from substance abuse treatment unit		(1) Certain first rank symptoms more commonly observed with schizophrenia subjects (2) CoIPD more associated with intense suspiciousness and fear of discovery (3) PCPIPD more associated with delusions of physical power, altered sensations, and unusual experiences
Iwanami et al[55] 1994 Japan	Methamphetamine	N = 104 Patients with DSM-III-R methamphetamine dependence and MIPD (delusional disorder) Recruited from inpatient unit	1 year	(1) Mean length of hospitalization was 2.5 months (2) 59% were discharged within 1 month (transient type) (3) 15% were hospitalized more than 3 months, 4% more than 1 year (persistent type) (4) In persistent type MIPD, non-visual/auditory hallucinations were more frequently observed than in transient type

[a]A decision tree based on DSM-IV criteria.
[b]DSM-III-R based.
Abbreviations: AIPD = amphetamine-induced psychotic disorder; BELD = best-estimate longitudinal diagnoses; BPRS = Brief Psychiatric Rating Scale; CIPD = cannabis-induced psychotic disorder; CGI = Clinical Global Impressions scale; CoIPD = cocaine-induced psychotic disorder; EIPD = ecstasy-induced psychotic disorder; HAM-D = Hamilton Rating Scale for Depression; ICD-10 = *International Classification of Diseases, 10th Revision*; MDMA = methylenedioxymethamphetamine; MINI = Mini-International Neuropsychiatric Interview; MIPD = methamphetamine-induced psychotic disorder; PANSS = Positive and Negative Syndrome Scale; PCP = phencyclidine; PCPIPD = PCP-induced psychotic disorder; PPD = primary psychotic disorder; PRISM = Psychiatric Research Interview for Substance and Mental Disorders; PSST = premorbid schizoid and schizotypal traits; SCID = Structured Clinical Interview for DSM-IV; SIPD = substance-induced psychotic disorder.

This issue is exemplified by a recent study examining psychotic symptoms among street methamphetamine users in Australia.[6] Using the Brief Psychiatric Rating Scale (BPRS), the authors found that almost a quarter (23%) of methamphetamine users had experienced a clinically significant symptom (at least moderate severity with a cut-off score of 4 or greater) of suspiciousness, unusual thought content, or hallucinations in the past year, while a further 52% reported experiencing mild symptoms that were not clinically significant (BPRS scores of 2 or 3). Nevertheless, clinical studies consistently report that patients with SIPD demonstrate high positive symptom scores on standardized psychosis rating scales.[15,42,44,46]

The current SIPD criteria consider hallucinations to be symptoms of psychosis only when they occur in the absence of insight, which is in contrast to the primary psychotic disorders. To suggest that in a substance user hallucinations with insight should be coded as "perceptual disturbances" seems an oversimplification. While the intent may be to eliminate the coding of "hallucinogen-induced psychosis" in which hallucinations are, by definition, a primary effect of the drug, the same phenomena in other classes of substances, while not uncommon, are clinically significant. Indeed, in a large study comparing early-phase primary psychotic disorders with concurrent substance use and SIPD, Caton and colleagues[44] found higher rates of visual hallucinations in the SIPD group (23.7% vs. 14.7%) and similar levels of auditory hallucinations between the groups (69.8% vs. 68.7%). Subjects in the SIPD group were more likely to be aware that they were experiencing psychotic symptoms and to interpret them as a manifestation of a mental disorder or substance abuse. Similarly, intact insight has been reported to be a common feature of most methamphetamine users with psychotic symptoms.[17] Thus, by not allowing those with insight to be diagnosed with SIPD, DSM risks excluding individuals with distressing symptoms from receiving psychiatric treatment, as their presentation may be downplayed or deemed clinically insignificant. This discrimination, based on the presence or absence of insight, implies evidence of a different etiology, course, or prognosis, which, to date, the authors are unaware of.

A further criticism of criterion A is its exclusion of other psychotic features, such as negative symptoms and disorganized speech. Negative symptoms have consistently been reported to occur in individuals presenting with SIPD, although they are generally less severe than those seen in patients with primary psychotic disorders.[15,44,46,47] Srisurapanont and colleagues[47] recently reported a 2-factor model for substance-induced psychotic symptoms in their multicountry study of patients admitted with methamphetamine psychosis. The first factor was a positive/disorganized syndrome marked by delusions, hallucinations, and disorganized speech, with the second factor being a negative syndrome, characterized by poverty of speech, psychomotor retardation, and flattened/incongruous affects. Thus, limiting criterion A to hallucinations and delusions alone may not capture the full spectrum of psychotic features found in SIPD. Further studies are clearly warranted to document the range and time course of psychotic features commonly associated with SIPD, as well as their relationship to specific psychoactive drugs.

Criterion B

By suggesting that SIPD occurs only during or within a month of intoxication or withdrawal, the current criterion B extols a narrow definition that serves to exclude a significant number of potential SIPD cases. Indeed, the DSM-IV notes that a certain, undefined level of psychosis may be expected with intoxication, when it states that "this diagnosis [SIPD] should be made instead of a diagnosis of substance intoxication or withdrawal only when the psychotic symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome."[56(p314)] The term *in excess* is confusing, as it is never defined, and the DSM-IV criteria for neither intoxication nor withdrawal list psychotic features as expected phenomena. By suggesting that psychosis can be an expected yet undefined feature of both intoxication and withdrawal, the DSM blurs the threshold for SIPD, leaving a significant degree of subjectivity when making the diagnosis.

The limited focus of the criterion on intoxication and withdrawal is of even greater concern. Crowley's Work Group review,[11] which appears in the DSM-IV Sourcebook, suggested that "the DSM-IV may avoid confusion among clinicians by clearly differentiating in text the very persistent drug-related disorders from those observed during intoxication and withdrawals."[(p102)] Concordantly, the DSM-IV-TR narrated that "for drugs of abuse, there must be evidence from the history, physical examination, or laboratory findings of dependence, abuse, intoxication, or withdrawal."[26(p338)] Inexplicably, both words, *abuse* and *dependence*, were omitted from criterion B.

So defined, psychotic episodes associated with SUD in the absence of intoxication fall outside SIPD criteria. This discounts the phenomenon of tolerance, which develops with ongoing substance use, such that individuals are *less* likely to have periods of intoxication. Whereas the evidence of persisting disorders due to the presence of SUD may have been unclear in 1988,[11] the omission of the words *abuse* and *dependence* has prevented clarification of the issue. Clinicians are left wondering how to code an individual with first-episode psychosis and concurrent SUD. Neither clinician- nor lay-administered diagnostic instruments offer assistance in making an accurate diagnosis "as they rely upon individual judgment rather than a built-in, systematized method of differentiation."[57] Indeed, given the current way the criteria are written, it is

likely that there is substantial underreporting of SIPD within epidemiologic surveys.

But is there evidence to support omitting SUD from the current criteria? If anything, SIPD has been shown to occur more frequently among individuals with SUD. For example, in a Japanese study of methamphetamine users, all the individuals who reported psychotic symptoms met criteria for either abuse or dependence.[17] In the United Kingdom, severe dependence on cannabis and psychostimulants was associated with a higher risk of psychosis in a sample of 3142 British prisoners,[58] while in an Australian study of 310 methamphetamine users, dependent users were 3 times more likely to have experienced clinically significant psychotic symptoms on the BPRS than their nondependent counterparts.[6] Within a U.S. emergency department setting, Caton and colleagues[44] reported that a diagnosis of "dependence on any drug" distinguished individuals with SIPD from those with a primary psychotic disorder, a finding that further supports the inclusion of SUD within the criterion.

Finally, by excluding SUD as an etiological factor, the criterion overlooks neuroimaging studies that support the notion that substances of abuse, especially when used chronically, change brain architecture and that these changes may take months to reverse, if at all.[59–61] The development of psychotic experiences with chronic use may reflect underlying changes in neurobiology that are distinct from psychoses associated with acute intoxication and may account for the extended episodes of psychotic symptoms documented in a minority of chronic users.[62] The criterion then, should reflect the possibility that SUD may be associated with de novo psychotic episodes and allow for the collection of evidence to either support or refute this notion.

Criterion C

Criterion C provides guidelines intended to distinguish substance-induced disorders from primary psychotic disorders. Again it omits SUD and, further, removes the option of coding "persistent states." The recommendation that evidence of a primary psychotic disorder includes symptoms persisting for "about a month" after substance cessation actually backtracks from DSM-III-R's assertion that cocaine- and amphetamine-induced delusional symptoms could last over a year.[63]

While substance-induced psychotic symptoms are typically transitory in nature, generally lasting less than a week in most cases,[6,55,64–66] there is a small, but growing literature suggesting that in a minority of chronic users, psychotic symptoms can last substantially longer than 1 month.[48,55] For example, Iwanami and colleagues[55] reported that 27% of 104 methamphetamine users admitted to a psychiatric unit with drug-induced psychosis (and with no evidence of schizophrenia) had symptoms lasting more than 1 month, despite ongoing abstinence and treatment with antipsychotic medication. Indeed, 17% had psychotic symptoms that lasted longer than 3 months. In one Taiwanese study of 174 methamphetamine users reporting psychotic symptoms, the authors reported that 30 experienced "persistent psychosis" after more than 1 month's abstinence, despite having no prior personal or family history of a psychotic disorder.[48] Similarly, in a Canadian study of 18 inhalant users (aged 15–29 years) with psychotic symptoms and no family or prior psychiatric history, 14 had persistent paranoid psychoses with auditory and visual hallucinations that required continuous neuroleptic treatment.[67] In the other 4 cases, while symptoms improved, recurrent episodes of psychosis were triggered by repeated inhalant use.

Such studies raise the issue of whether chronic use of psychotomimetic drugs can elicit a long-lasting drug-induced psychotic syndrome or precipitate the development of a primary psychotic disorder in at-risk individuals. Studies that have examined premorbid characteristics of individuals with SIPD suggest that personality traits may play a contributory role. For example, methamphetamine users who developed psychosis were found to have significantly more premorbid schizoid and schizotypal personality traits than nonpsychotic methamphetamine users, with schizoid/schizotypal trait scores positively correlated with symptom duration.[48] Tsuang and colleagues[68] have also reported significantly more schizoid or paranoid personality traits among drug users with prolonged psychosis (more than 6 months) compared to drug users without psychosis and those with briefer psychotic episodes. However, individuals with cannabis-induced psychosis have been found to have significantly fewer premorbid schizoid traits than patients with schizophrenia, although they did have more antisocial traits.[49] Such studies suggest that individuals who develop SIPD (particularly those with prolonged symptoms) may share an underlying vulnerability that is common to other primary psychotic disorders.

It is arguable that making an accurate diagnosis by using the current criteria is challenging for clinicians regardless of the timeframe applied, especially since polydrug use is common among drug users[13] and since individuals may use several substances in an intensive and chaotic fashion, simultaneously or consecutively. Other potential confounds that complicate the diagnostic picture include a recent history of significant psychosocial stressors, such as trauma and/or homelessness, and the early use of antipsychotic agents. From a toxicologic perspective, the arbitrary 4-week timeline contradicts data relating to the clearance of substances, such as cannabis, which is detectable in the urine up to 46 to 77 days after last consumption.[69] This prolonged excretion suggests that certain substances (like cannabis) that persist in fatty tissue for extended periods may have psychotogenic effects that extend well beyond the 4-week period.

It is often practically difficult to ensure periods of abstinence that are sufficient to reliably differentiate

between substance-induced and primary psychotic disorders. Indeed, in a study of 165 male patients with chronic psychosis and cocaine abuse or dependence, Shaner and colleagues[70] reported that only 18% were given a definitive diagnosis on assessment. A clear diagnosis could not be reached in the other 135 cases because of 1 or more sources of diagnostic uncertainty, including insufficient periods of abstinence (78%), poor memory (24%), and inconsistent reporting (20%). In addition, reassessment at 18 months led to definitive diagnoses in only 12 additional cases. This study highlights the difficulties associated with relying solely on any specific timeframe to clarify diagnostic uncertainty and questions the clinical validity of the current diagnostic criteria.

Recently, Caton and colleagues[39] reassessed a sample of 319 individuals with early-phase psychosis and substance use at 1 year and found that the diagnostic picture remained relatively stable for the majority of patients. However, 25% of those previously diagnosed with SIPD subsequently met criteria for a primary psychotic disorder. These patients had poorer premorbid functioning, less insight, and a more extensive family history of psychiatric illness than patients with a stable diagnosis of SIPD. The change in diagnosis was largely a result of persistent psychotic symptoms in the absence of substance use. Using data from the Danish Psychiatric Central Register to follow up 535 cases of cannabis-induced psychosis over an average of 5.9 years, Arendt et al.[45] found that 77% experienced further psychotic episodes, with 54% developing persistent psychotic conditions. Forty-five percent were later diagnosed with schizophrenia-spectrum disorders. Together, these studies emphasize that a diagnosis of SIPD should not be treated as a singular episode, and ongoing follow-up and review should be routinely offered.

While the spirit of criterion C is to differentiate between a primary psychotic disorder and a substance-induced episode, it offers little coding options to describe someone with a primary psychotic disorder who has relapsed while using a psychotogenic substance. By disavowing the diagnosis of a superimposed substance-associated relapse on the background of a primary psychotic disorder, is it DSM-IV's assertion that the 2 conditions are synonymous? Does a substance-associated psychotic relapse in an individual with an otherwise medically stable (e.g., depot antipsychotic medication) chronic psychotic illness have a similar etiology or clinical course to that of a nonsubstance-associated psychotic relapse? Existing research is limited, and the current criteria hinder collection of further epidemiologic data critical to exploring this issue.

DISCUSSION

As written, the narrowed definition of substance-induced psychosis is diagnosable only in individuals who are intoxicated or in withdrawal, with symptoms lasting less than 4 weeks. As a result, since 1994 individuals with psychotic symptoms and co-occurring SUD are likely to have been categorized as (a) substance-induced psychosis with onset during intoxication, (b) schizophreniform disorder, or (c) psychosis, not otherwise specified. This system has major implications for the management of this population, as no consensus clinical guidelines currently exist for the treatment of SIPD. Thus, clinicians remain uncertain as to when, with what, and for how long they should offer treatment and whether follow-up is a necessary requirement. More disturbing, young patients risk being diagnosed with a primary psychotic disorder (including schizophreniform or even schizophrenia) and their substance use being overlooked or minimized. This limitation has implications for treatment and prognosis as well as for individuals' understanding of their illness.

Indeed, despite the difficult diagnostic challenge faced by clinicians and researchers in accurately differentiating SIPD from primary psychotic disorders with concurrent substance misuse, there has been limited research conducted since 1992 that rigorously assesses the validity of DSM-IV's SIPD criteria. The bulk of publications have been case reports, with few studies, until relatively recently, examining the prospective outcomes of individuals diagnosed with SIPD. This work has been further aided by the development of a specific diagnostic instrument (the Psychiatric Research Interview for Substance and Mental Disorders) that has improved the reliability of making a SIPD diagnosis.[71] However, the issue of a prolonged drug-induced psychosis continues to remain a contentious issue, with most of the data derived from Japanese or Taiwanese samples. The majority of other studies have been epidemiologic in nature, thus rigorously adhering to the current DSM criteria. Treatment studies have been even rarer, with only 3 small randomized controlled trials conducted.[43,51,52] Evidence-based clinical guidelines are lacking, and there is no consensus regarding when to commence antipsychotic treatment or for how long. This limited literature highlights the need for a more systematic program of research that particularly focuses on the epidemiology, clinical characteristics, treatment options, and prognosis of SIPD (for each substance type) as well as its genetic and neurobiological underpinnings.

Based upon the current evidence base, we propose a number of revisions to the SIPD criteria (Table 3). To begin, we propose changing the title from substance-induced psychotic disorder to substance-associated psychotic disorder (SAPD). This reflects the growing literature highlighting an association between substance use (particularly cannabis and stimulant use) and psychosis onset, while acknowledging that the underlying etiology still remains undetermined. In addition, as Shaner and colleagues[70] discovered, it is exceedingly difficult to reliably differentiate substance-induced psychoses from

Table 3. Proposed Substance-Associated Psychotic Disorder Criteria

A. Prominent hallucinations or delusions
B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):
   (1) The symptoms in Criterion A developed within a month of SUD or Intoxication or Withdrawal;
   (2) Medication use is etiologically related to the disturbance
C. The disturbance is not better accounted for by a Psychotic Disorder that is not substance-induced. Evidence that the symptoms are better accounted for by a Psychotic Disorder that is not substance-induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time after the cessation of an SUD (e.g., greater than 6 months) or beyond a period of withdrawal or intoxication
D. If there is evidence of a preexisting, independent, non–substance-induced Psychotic Disorder (e.g., a history of non–substance-related episodes) preceding the disturbance, the psychotic episode was almost certainly induced by the substance in question (e.g., the disorder had been stable prior to substance use)
E. The disturbance does not occur exclusively during the course of delirium

Note:
With Negative Symptoms
With Onset During SUD: if the symptoms develop in the context of an SUD and the criteria for intoxication or withdrawal are not met
With Onset During Intoxication: if the criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome
With Onset During Withdrawal: if the criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, a withdrawal syndrome
Brief Episode: if the symptoms are present for less than 4 weeks
Persistent Episode: if the symptoms persist for more than 4 weeks

schizophrenia-spectrum disorders, and it is clinically challenging, if not impossible, to accurately conclude that the presentation unreservedly reflects a substance-induced state. To this end, a diagnosis of SAPD implies an association between state and substance, rather than causation, which more accurately reflects our current understanding of the interplay between psychotic symptoms and substance use.

Our proposed revisions to each criterion are discussed below; they are accompanied by 4 illustrative case vignettes that exemplify how the updated criteria potentially clarify diagnostic issues.

> ***Case 1.*** An 18-year-old female patient presents distressed with disturbing visual hallucinations, which she attributes to her 5-year history of near daily solvent abuse. After 2 weeks of antipsychotic treatment, the visual hallucinations persist, although she continues to believe that they are related to the solvent abuse. During her inpatient stay, she abstains from all psychotogenic substances and is eventually discharged 2 weeks later, symptom free.

In the revised criterion A, the definition of psychosis has been broadened, eliminating a lack of insight to hallucinations. While there is growing evidence that some individuals with SIPD also present with disorganized speech (compare with criteria for brief psychotic disorder), this finding requires further exploration. Similarly, "negative symptoms" should be considered as a potential specifier, as there is limited but growing evidence[15,44,46,47] supporting the presence of a substance-associated negative syndrome. Thus, whereas previously the female patient in Case 1 would have been diagnosed with "solvent-induced perceptual disturbances," the insightful solvent user with distressing visual hallucinations clearly has a "solvent-associated psychotic disorder" according to our revised criterion A.

> ***Case 2.*** A 23-year-old woman presents in an acutely agitated state, complaining of persecutory delusions and auditory hallucinations. She has no prior history of a psychotic disorder. She has smoked cannabis daily since the age of 14 but recently reduced her level of use. After 4 weeks of antipsychotic treatment as an outpatient, she continues to have psychotic symptoms despite having several clean urine drug screens. Her symptoms finally remit 6 weeks later, 10 weeks after her initial presentation.

In the revised criterion B, we recommend the expansion of criterion B specifiers to include "with onset during SUD," which would incorporate episodes that occur in the context of either reduced or increased substance use (not necessarily resulting in withdrawal or intoxication). While several substances continue to be associated with psychotic features during times of intoxication or withdrawal, SUD is a risk factor for the development of SAPD and the criterion should acknowledge this. Case 2, that of a chronic user with no prior history of a psychotic disorder cutting back her cannabis intake, would be diagnosed as having a "cannabis-associated psychotic disorder, with onset during an SUD." Irrelevant under this revision is the fact that she is neither intoxicated nor in withdrawal.

> ***Case 3.*** A 28-year-old man presents with his fourth psychotic episode following a 1-month relapse of daily intravenous methamphetamine use. The initial psychotic episode, at the age of 24, was preceded by a 6-month period of near daily methamphetamine use. He experienced persecutory delusions regarding organized crime, which remitted after 2 weeks, and his antipsychotic medication was discontinued soon thereafter. Subsequently, he relapsed twice with similar psychotic episodes, each preceded by ever briefer periods of methamphetamine use. His most recent episode is again characterized by persecutory delusions regarding organized crime. The psychotic symptoms improve after 6 weeks of inpatient care, although he maintains circumscribed delusional beliefs for a further 2 months.

The revised criterion C defines evidence of a preexisting psychotic disorder as that which has either the presence of symptoms preceding the substance use or the persistence of symptoms beyond a 6-month period of abstinence. More in keeping with the DSM-III-R, the 6-month timeline allows for adequate assessment and

follow-up of those diagnosed with SAPD before formally making a diagnosis of schizophrenia. In our revised criteria, specifiers also allow for the recording of "brief episodes" (less than 4 weeks) versus "persistent episodes" (longer than 4 weeks). Under this revision, Case 3, that of a person with a history of psychotic episodes strongly linked to a precipitant, yet with a time course falling outside the DSM-IV guidelines, suggests a diagnosis of "methamphetamine-associated psychosis, with onset during SUD, persistent episode."

> ***Case 4.*** A 22-year-old man with schizophrenia, adherent on his antipsychotic regimen, presents with the belief that "some people" have bugged his telephone and monitor all his conversations and watch him shower. Six months prior to his presentation and while his schizophrenia was in remission, he began smoking cannabis daily, despite having never smoked before. The delusions are similar to those present during his first psychotic episode at the age of 18.

Finally, while acknowledging that Case 4 illustrates a potentially contentious issue, we address the question of how to code a substance-associated psychotic episode in the context of a primary psychotic disorder. In Case 4, the young man suffering from schizophrenia is stable and in remission until he relapses while abusing cannabis. This raises the issue of whether the relapse relates to an exacerbation of the underlying psychotic illness or potentially reflects a substance-associated psychosis with a differing neurobiological etiology. To date, we are not aware of any literature that has directly addressed this question and therefore present 2 potential coding options so that the impact of substances on relapse in those with primary psychotic disorders can be further characterized.

The first option would be the addition of criterion D, included in Table 3, so that the diagnosis in Case 4 might be recorded as "cannabis-associated psychosis, with onset during SUD, brief episode, superimposed on schizophrenia." Conversely, in lieu of criterion D, a specifier of "with substance-associated episode" might be added to the diagnostic criteria of primary psychotic disorders so that Case 4 might be recorded as "schizophrenia, paranoid type, with cannabis-associated episode." While there are pros and cons to either option, we are hopeful that this discussion will generate a lively debate on the issue, and encourage further research into the area.

CONCLUSIONS

There has been limited SIPD research conducted to date, and the validity of the DSM-IV diagnostic criteria has yet to be rigorously examined. There remains a striking paucity of information on the outcome, treatment, and best practice for substance-associated psychotic episodes; further work is clearly required before the advent of DSM-V. We have proposed an alternative, broader classification that implies association rather than causation and better reflects the current, although limited evidence base. We hope that such criteria will aid clinicians working at the coalface of acute psychiatry to clarify the diagnosis of SAPD and stimulate research efforts to improve current understanding of the assessment, treatment, and prognosis of substance-associated psychotic states.

Drug names: haloperidol (Haldol and others), ketamine (Ketalar and others), methamphetamine (Desoxyn), olanzapine (Zyprexa).

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