Comorbidity between substance use disorders and psychiatric conditions

Marc A. Schuckit

VA San Diego Healthcare System, San Diego, CA, USA

ABSTRACT

Aims To review information relevant to the question of whether substance-induced mental disorders exist and their implications. **Design and method** This paper utilized a systematic review of manuscripts published in the English language since approximately 1970 dealing with comorbid psychiatric and substance use disorders. **Findings** The results of any specific study depended on the definitions of comorbidity, the methods of operationalizing diagnostic criteria, the interview and protocol invoked several additional methodological issues. The results generally support the conclusion that substance use mental disorders exist, especially regarding stimulant or cannabinoid-induced psychoses, substance-induced mood disorders, as well as substance-induced anxiety conditions. **Conclusions** The material reviewed indicates that induced disorders are prevalent enough to contribute significantly to rates of comorbidity between substance use disorders and psychiatric conditions, and that their recognition has important treatment implications. The current literature review underscores the heterogeneous nature of comorbidity.

Keywords Alcoholism, depression, psychosis.

Correspondence to: Mark A. Shuckit, Department of Psychiatry (116 A), University of California, San Diego and the VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161–2002, USA. E-mail: mschuckit@ucsd.edu

INTRODUCTION

Most diagnoses in medicine are based on a combination of symptoms, their time-course and a threshold beyond which the syndrome is felt to be clinically relevant [1]. No single indicator is likely to be sufficient to establish a diagnosis because these are rarely unique to one syndrome. For example, in medicine, chest pain could reflect a broken rib, an invasive tumor, a consequence of pneumonia or a myocardial infarction. Diagnosis and treatment cannot rest with the pain itself, but this symptom is used as an entrée into a differential diagnosis that considers additional problems over time, along with biological tests, before appropriate treatment can be instituted. Similarly, in psychiatry, sadness could reflect grief, thyroid disease, adrenal abnormalities or a reaction to chronic pain, in addition to serving as the central signal for a potential major depressive episode, the depressive phase of manic-depressive disease or a consequence of repeated intake of high doses of depressant drugs such as alcohol. Psychiatry is especially vulnerable to the non-specificity of symptoms, as there are few (if any) biological tests that are sensitive and specific enough to establish a diagnosis.

Potential problems with the diagnostic process increase almost exponentially when substance use disorders (SUDs) and psychiatric syndromes occur together, as a reflection of at least four broad issues [2–4]. First, combinations of SUDs and psychiatric disorders may represent two or more independent conditions, each of which is likely to run the distinct clinical course relatively unique to that disorder. Here, both conditions must be treated comprehensively. This combination could occur through chance alone (roughly the prevalence of one disorder multiplied by the prevalence of the other), or be a consequence of the actions of the same predisposing factors (e.g. stress, personality, additional psychiatric disorders, childhood environment and genetic influences) affecting the risk for multiple conditions [5]. Secondly, the first disorder could influence the development of the second condition in a such manner that the additional disorder then runs an independent course. For example, the frequent use of high doses of substance could unmask a latent predisposition toward a psychiatric disorder or cause permanent physiological changes in the brain that result in long-term or permanent psychoses, depression, and so on [5–7]. Again, both conditions must be treated

for as long as necessary. Similarly, a psychiatric disorder (e.g. mania) could increase the risk for heavy and repetitive use of substances, an SUD that might continue even when the pre-existing psychiatric condition is appropriately treated or remits. A third relationship could be seen if the second condition developed through an effort of the patient to diminish problems associated with the first syndrome. Here, for example, a person might escalate the use of substances and develop an SUD in an attempt to alleviate feelings of depression, or to decrease side-effects of psychiatric medications. Here, while the substance use disorders might become a long-term problem, the excessive use of alcohol or an illicit drug might disappear when the pre-existing clinical syndrome is addressed appropriately.

This review focuses on a fourth category of contributors to the high prevalence of psychiatric comorbidities seen in individuals with SUDs. Some syndromes may be temporary psychiatric pictures (e.g. psychosis with features resembling schizophrenia) seen as a consequence of intoxication with specific types of substances (e.g. stimulants, such as amphetamines and cocaine) or withdrawal conditions (e.g. depressive syndromes with cessation of stimulants). These substance-induced syndromes represent an important challenge to both researchers and clinicians attempting to understand more about the complex relationship between psychiatric and substance-related disorders.

The distinction between the types of comorbidities, each of which are likely to operate in some patients, has important implications [8,9]. The etiologies may be different [10] (a factor of importance for research), and several categories, including substance-induced disorders, are likely to have distinct clinical courses and responses to treatment [11]. The following sections discuss comorbidity, with an emphasis on substance-induced disorders, by addressing: the impact of methodology on research results; evidence that substance-induced disorders exist; the clinical and research relevance of these conditions; and some suggestions for research questions that might be addressed in the process of preparing for the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-V).

METHODOLOGICAL ISSUES THAT AFFECT RESULTS

Different definitions of comorbidity

Comorbidity has been defined in a variety of ways. Some studies place an emphasis on 'pure psychiatric diagnoses', defined as a psychiatric condition observed in the absence of any other major diagnosis during the same year [12]. More classically, multiple diagnoses have been placed into a primary versus secondary approach [13], where the first condition to develop is labeled as 'primary', a notation that depends upon chronology, not necessarily cause and effect. Other authors have labeled as primary the major reason for clinical care.

The independent versus substance-induced distinction is an extension of the primary/secondary approach. It was developed in recognition that a psychiatric syndrome (e.g. a major depressive episode) might also be identified during periods of abstinence, and that labels should not be based solely on initial chronology [9,14]. Therefore, the ability to spot independent disorders should be enhanced.

Most data on comorbidities were developed regarding SUDs and Axis I conditions such as depressive syndromes, and these will be emphasized here. Of course, comorbidity of SUDs with each other and with Axis II personality conditions is also relevant [15], but is beyond the scope of the current review.

Operationalization and evaluation of the diagnostic criteria

A number of questions arise regarding how the labels are used within a research protocol. For example, does the project require that the specific type of drug must be relevant to the specific comorbid diagnosis? This is important, because some drugs (e.g. intoxication with alcohol and sedative hypnotics) can cause some temporary conditions (e.g. depression), but are less likely to cause others (e.g. mania) [16]. A second issue is whether the diagnosis is required to be associated with great distress or impairment, or if a simple endorsement of the symptoms by a respondent is enough to make a diagnosis [17]. Obviously, without this requirement the inclusion of many minor symptoms and life problems could markedly expand the number of people diagnosed. Thirdly, a similar problem can occur if the criteria did not include the need for some problems to have occurred repeatedly (an issue relevant to many of the criterion items for SUDs), or did not determine if the items clustered together during the relevant period. Studies also vary regarding their emphasis on syndromes occurring in the last year versus during the life-time, with the combination of time-frames important for the primary versus secondary or induced versus independent approaches. It is also important to note whether the full diagnostic syndrome is required for establishing the ages of onset and for remission, or if a diagnosis is considered valid if only some symptoms are present. In the absence of a full syndrome, the age of onset is likely to be much younger, but the process might be like determining the onset of major depression as the first time a person was ever sad. Differences across studies on any one of these items are likely to have a large impact

on the results regarding the incidence, time course, and optimal treatment of comorbidities.

An additional and very important research issue relates to the types of interviewers employed and their level of supervision. The problem here is that different studies can have different, but complementary, assets and liabilities. Large-scale epidemiological investigations, such as the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), gather data on thousands of subjects over a very short time, and can be excellent measures of patterns of problems in a wide range of people in the general population. However, such studies require large numbers of non-clinician interviewers who can have difficulty interpreting the relevance of some complaints (e.g. mania), and demonstrate problems determining whether the symptoms were relatively mild and transitory (e.g. for some simple phobias) versus those relevant to a diagnosis. The need for so many interviewers also means that the problems reported by subjects are less likely to be reviewed by clinicians, a time-consuming but useful process used in the Collaborative Study on the Genetics of Alcoholism. The clinician reviewer can then encourage interviewers to gather additional information about the clinical condition, rather than having them adhere rigidly to a fully structured interview. On the other hand, the high level of structure in the research instruments used by NESARC minimize differences between interviewers. However, the approach that is necessary for large-scale studies may make it difficult to gather more detailed information required for the more subtle distinctions, such as those between induced and independent depressions.

Other problems reflect the approach used to deal with what appear to be multiple diagnoses in the same person. This occurs, for example, when a subject endorses depressive symptoms, reports panic attacks and describes discomfort in social situations. In some studies these are listed as three separate diagnoses, but others establish a hierarchy, searching for one overarching diagnosis (e.g. major depression) that might explain the other complaints (e.g. temporary panic attacks and feelings of social discomfort).

The interview used in the protocol

Some interviews were developed to gather information quickly on substance-related issues from a large number of diverse subjects, using hundreds of interviewers (e.g. the Alcohol Use and Associated Disabilities Interview Schedule for DSM-IV (AUDADIS–DSM-IV) [18]. Others were constructed for large populations, but with an emphasis on non-substance-related conditions, such as the Diagnostic Interview Schedule (DIS), the Composite International Diagnostic Interview (CIDI) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID–IV) [19,20]. With any of these measures, unless closely supervised lay interviewers may have difficulties distinguishing periods of situational excitement or substance-related irritability from mania, or whether driving while impaired with alcohol occurred (i.e. what amount of alcohol was consumed over what period of time followed by driving how many hours later?). Thus, such epidemiological interviewer-based instruments are ideal for large epidemiological studies, but might exaggerate the rates of psychiatric disorders and SUDs by reporting conditions that might not meet a full and clinically relevant syndrome. These interviews might not be optimal for exploring more complex questions such as comorbid conditions, especially with regard to substance-induced disorders.

Several instruments have been developed to overcome some of these problems, but are less efficient and can be too expensive for use in large epidemiological surveys. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview was created to help distinguish primary versus secondary or substance-induced versus independent conditions, and to gather detailed information about substance-related issues [21,22]. Interviewers are trained to use a time-line approach to establish the age of onset of dependence, periods of abstinence and ages of onset of Axis I syndromes. The SSAGA has a semistructured format to facilitate such determinations, using lay interviewers who probe for additional information along with close review by editors and a final diagnosis established through a clinician-based evaluation of all data sources. The semistructured nature encourages interviewers to gather additional information relevant to the clinical intensity, duration, and clustering of symptoms, with editors often asking the interviewer to return to the research subject to gather more information.

The Psychiatric Research Interview for Substances and Mental Diseases (PRISM) [23,24] can also help evaluate independent and induced psychiatric conditions. This instrument places sections dealing with drugs and alcohol early in the interview, and an effort is made to establish the age of onset of substance-related and psychiatric syndromes based on the age at which the full disorder was present. The interview is structured to optimize interpretation of substance-induced versus independent conditions, but gathering of additional information and clinician review is not always used.

Additional research attributes likely to impact on results

The population selected for study (patients, their relatives, general populations and respondents to an advertisement) can influence results. However, no one study or single group of subjects can give the 'true answer' regarding the prevalence and patterns of psychiatric and SUDs.

Rather, it is important to evaluate patterns across different populations.

The timing of the evaluation is also important. For example, rates of comorbid psychiatric syndromes are likely to be temporarily elevated if substance-dependent subjects are interviewed during intoxication, withdrawal or the first several weeks of abstinence [25]. These are times of highest prevalence of substance-induced disorders.

It is also important to gather additional sources of data about subjects whenever possible. These include clinician reviews of all available information on a patient [26], using additional informants (e.g. a spouse) regarding the subject and urine toxicology screens or state markers of heavy drinking. These can be key in determining whether, for example, depressive symptoms reported in a follow-up were truly independent of substance use. In addition, evaluations of risk factors for comorbidity require consideration of assortative mating in the families, a factor that increases comorbidity in the offspring, and such data often require interviewing relatives as well as the subject [27].

DO SUBSTANCE-INDUCED DISORDERS EXIST?

Psychiatric nosologies have traditionally emphasized the importance of recognizing temporary psychiatric conditions observed in the context of biological influences. These include auditory hallucinations during Cushing's disease or hypothyroidism that may not be schizophrenia, intense sadness in someone taking beta-blockers that may not be a typical major depressive episode. Similarly, psychiatric symptoms seen only in the context of substance intoxication and withdrawal can have distinct prognoses and treatments [9,23]. The goal of this section is to emphasize that there is enough support for the existence of substance-induced disorders for them to be included in the DSM. Thus, this is not a meta-analysis nor a detailed contrast and comparison of all pro and con research.

Data supporting stimulant-induced psychoses

Temporary schizophrenia-like conditions of hallucinations (predominantly auditory) and/or delusions (usually paranoid) developing without insight and observed in a clear sensorium can be induced by stimulants. They should be distinguished from the life-long schizophrenic disorders, as the former are likely to require only short-term antipsychotic medications, while schizophrenia often necessitates such drugs for many years [28].

Schizophrenic-like psychoses can be induced in the laboratory with stimulants [29]. Angrist and colleagues [30,31] administered up to 50 mg of amphetamine per hour in nine healthy subjects who became psychotic within 7–45 hours, and usually following 200–300 mg of amphetamines. All recovered within 6 days of abstinence. Bell [32] gave doses of amphetamines necessary to increase blood pressure by 50% to 16 subjects, reporting psychoses in 12, with all disappearing with abstinence. Griffith [33] used a similar protocol in four males with no prior psychiatric or substance use history, demonstrating psychotic syndromes in all, usually with 120–250 mg of the drug, and reporting full recovery with abstinence.

Additional support for temporary stimulant-induced psychoses resembling schizophrenia comes from descriptions of clinical samples and surveys of populations. Following the first known report of temporary psychoses with stimulants [34], 'epidemics' of these syndromes have been recorded after the Second World War in Japan and Germany, with subsequent case descriptions published from Europe, Asia, and the United States [35–38]. Psychotic symptoms are estimated to occur at some time in about 40% of amphetamine-dependent patients, especially with higher doses [16,23]. Stimulant-induced psychoses have been reported with a wide range of stimulants, and may be a good model for evaluating evanescent neurochemical changes likely to be similar to more permanent changes observed in schizophrenia [35,36,38,39]. Stimulant-induced psychoses are *very likely to clear* within several days to about a month of abstinence [31–33,37]. Only 1–15% of patients with stimulant-induced psychoses maintain some psychotic symptoms after a month. As described in the Introduction, these could reflect the fact that 1% or so of people in any group will develop schizophrenia, or could be the consequence of the precipitation of longer-term psychotic disorders in predisposed individuals. Thus, a person with schizophrenic relatives or someone in the early phases of this disorder is likely to deteriorate when they take stimulants, a process that underscores the heterogeneity and complexity of the relationships between SUDs and schizophrenic symptoms [6,29,37,40,41]. This might contribute to reports that up to 60% of schizophrenics in treatment have histories of abuse or dependence on illicit drugs such as amphetamines and cocaine [4,6,42,43]. It is also possible that heavy use of stimulants might cause more long-lasting, and hypothetically even permanent, neurochemical changes associated with long-term psychotic disorders in a small number of individuals, even if not so predisposed. However, permanent psychoses caused solely by stimulants are likely to be fairly rare and, thus, difficult to study. In any event, if hallucinations and/or delusions without insight continue after a month to 6 weeks of abstinence, the symptoms may well represent an independent psychotic disorder that requires long-term antipsychotic medications.

The symptoms observed in stimulant psychoses closely resemble those seen in schizophrenia. Therefore, the best approach to initially establishing a working diagnosis might rest with a chronology-based time-line [32,36,37,39]. Regarding specific symptoms, paranoid delusions have been reported in between 25% and 75% of stimulant-induced psychoses, auditory hallucinations in 50–85%, ideas of reference in 15–60%,and Schneiderian first-rank symptoms in 50% in some surveys [29,36,37]. Negative schizophrenia-like symptoms may be seen in ~30% of such subjects [32,44].

The data supporting a cannabinoid-induced psychosis

Laboratory observations are limited to the documentation that intoxication with this drug can produce feelings of derealization, depersonalization and paranoia [45]. Therefore, most support for temporary cannabinoid-induced psychosis comes from clinical descriptions of temporary hallucinations and/or delusions without insight in cannabinoid users in India, Asia, the United Kingdom, South Africa, New Zealand and the United States [46–48]. Of course, some cases may represent acute toxic drug effects associated with delirium, although most developed in a clear sensorium, and some might reflect precipitation of psychotic syndromes in predisposed individuals [49]. However, most studies indicate that the auditory hallucinations and paranoid delusions, including Schneiderian first-rank symptoms [50], are very likely to disappear within several days to a month with abstinence.

Cannabinoids are also likely to enhance the risk for schizophrenia in people carrying a predisposition. A 15-year follow-up of ~50 000 Swedish military conscripts demonstrated a 2.4–6-fold increased risk for later hospitalization for schizophrenic-like disorders in individuals who used marijuana at baseline [7,51]. However, none of the heaviest users developed schizophrenia, and many who became psychotic were occasional users or life-long abstainers. In addition, a 3-year follow-up of about 4000 people in the Netherlands reported a 2.8-fold increased risk for subsequent schizophrenia in cannabinoid users [52], with similar results in New Zealand [53]. Support for the conclusion that these figures represent precipitation of illness in predisposed people rather than cannabinoid caused psychoses in the general populations comes from observations that increased marijuana use across cohorts is not associated with a greater life-time risk for schizophrenia across such cohorts or in countries with higher, compared to lower, marijuana use rates [54]. As described with stimulants, if true psychotic symptoms in a clear sensorium and without insight remain after 4–6 weeks of abstinence, the condition may represent a long-term and potentially permanent psychosis such as schizophrenia.

Before moving on to substance-induced depressive syndromes, it is important to emphasize that temporary substance-induced psychoses are also observed with some additional drugs including alcohol and, perhaps, phencyclidine [16,55,56]. Rates of alcohol use disorders are also evaluated among schizophrenics [56], and there is a complex relationship between schizophrenia and nicotine dependence [57,58]. A review of these interesting and complex relationships must await additional papers.

Evidence supporting substance-induced mood disorders

Temporary depressive symptoms have been reported in the context of intoxication or withdrawal for nicotine, cannabinoids, opioids, hallucinogens and other drugs of abuse [16,59]. Because the question at hand is whether it is possible that substance-induced disorders might exist, this section focuses on the drug with the most available data, alcohol, but briefly mentions additional substances where appropriate.

Laboratory experiments have demonstrated that alcohol affects mood. One study of 10 subjects who consumed alcohol every 2 hours throughout the day (up to 25 standard drinks in 24 hours) reported that most developed depressive syndromes, including at least four with suicidal ideation who dropped out during the first week. All depressions cleared with abstinence [60]. In a second series of studies, 14 subjects paid to drink heavily for several weeks demonstrated increasing levels of depression, guilt and feelings of anxiety, and all depressions disappeared with abstinence [61,62]. Another investigation of 12 volunteers offering free access to alcohol over 7 days reported temporary depression and anxiety in most subjects [63], while a study of women reported that the consumption of two or more drinks during a session was associated with mild depressive symptoms both during the experiment and the next morning [64].

SSAGA interviews with clinician review of diagnoses have documented that >40% of alcoholics have ever fulfilled criteria for major depressive-like syndromes, with almost 70% of these being substance-induced disorders. These include data from families in the six Collaborative Study on the Genetics of Alcoholism (COGA) centers, two Native American groups [9,14,65,66] and alcoholics entering treatment [67]. However, a large national epidemiological study using the AUDADIS and lay interviewers without clinical supervision reported high rates of depression in alcoholics, but noted that few were substance-induced [18]. These divergent results probably reflect different methods across studies as described in the section on methodological issues.

Additional support for the relevance of substance-induced mood disorders comes from prospective studies that suggest that heavy drinking at time 1 is likely to

predict depressive symptoms at time 2. A 6-year follow-up of 176 subjects reported that drinking predicted an increased number of subsequent transitions from functioning well to periods of depression (perhaps reflecting substance-induced mood disorders), while individuals with prior (but not currently active) alcoholism had no increased number of transitions to depression over time [68]. Active alcoholism among depressed individuals made it less likely that they would demonstrate transitions to a euthymic mood. Another prospective study reported that heavier drinking during month 2 predicted depressive symptoms during month 3 [69]. In addition, 3- and 12-month follow-ups of almost 200 alcoholics revealed that only those who had returned to drinking were likely to demonstrate depressions [67], while a longitudinal study of more than 700 adults reported that patterns of higher alcohol use during earlier follow-ups predicted a higher prevalence of depressive symptoms at subsequent contacts [70]. Finally, a follow-up of young subjects found no relationship between earlier heavy drinking and later AUDs, unless the individuals continued heavy drinking [71].

Prospective studies of populations at high risk for depression or alcoholism also generally support the existence of substance-induced mood disorders. First, despite evidence that some people may drink (not necessarily to the point of problems) in response to both positive and negative affect [72,73], two follow-up studies of teenagers who had major depressive episodes reported no heightened risk for alcohol or drug dependence over the subsequent decades, despite a high prevalence of future depressions [74,75]. The results might also indicate that independent major depressions tend to run a true course, and are not usually associated with later alcoholism unless, perhaps, there are alcohol-dependent relatives as well.

Some studies of offspring of depressed subjects and those with early shyness or psychological symptoms report an increased subsequent risk for substance-related problems [17,76,77], but others noted no increased risk for AUDs in children of depressed individuals [78–80]. Relationships are complex, may differ across the sexes, and positive studies may include subjects with additional family histories of alcoholism or SUDs [80,81]. Similarly, several prospective studies of teenagers reported that young heavier drinkers or children of alcoholics may have increased depressive symptoms [82,83], but others disagree and note these subjects were no more likely to develop mood problems or major depressive episodes than controls [79,84,85]. The negative studies include an evaluation of ~1000 16–25-year-old subjects in New Zealand, where earlier drinking patterns were predictors of alcohol-related outcomes but not of depressive disorders [86]. A prospective evaluation of two generations of 453 families of alcoholics and controls noted that an alcoholic relative predicted higher rates of alcohol use disorders, but not independent major depressive episodes [16,80,87–89].

When substance-induced mood disorders are identified, they are likely to disappear soon after abstinence, a situation not seen with independent depressive episodes. Thus, overall continued abstinence in alcoholics is likely to be associated with a decrease in depressive symptoms [90–93]. For example, follow-up of alcoholics with substance-induced mood disorders reported that the proportion with marked depressive symptoms decreased from 42% to 6% with 1 month of abstinence [67]. A separate study of unmedicated male alcoholics documented that, for those with induced depressions, an average Hamilton Depressive score of 16 after 1 week of abstinence decreased to a score of six after 4 weeks dry, while similar decreases are not seen for subjects initially identified as having independent major mood disorders [25,94]. Similarly, in another investigation the proportion of alcoholics with major depressive-like symptoms decreased from 67% to 13% over a month, without antidepressant treatment [95], findings supported by several other clinical observations [93,96–100]. In addition, 85% of those with alcohol-induced mood disorders ran the course predicted regarding the temporary nature of the symptoms [92], and an 18-month follow-up of in-patients dependent upon a variety of drugs or alcohol showed that the course of substance-induced depressions was different from independent mood disorders. A tendency toward diminution or disappearance of depressive symptoms with abstinence has also been reported for patients entering care for stimulant or opioid dependence [101–108]. At the same time, the diagnosis of induced depressive episodes cannot be based on cross-sectional symptom patterns, because depressive symptoms in the context of heavy drinking are almost identical to those seen during independent depression [9,109], and can include suicidal ideation.

There are several validators of the accuracy of timeline-based notations of substance-induced mood disorders. First, such substance-induced disturbances are more likely than independent disorders to diminish and disappear with time alone [25,67,92]. Secondly, an elevated risk for independent mood disorders in relatives may be only seen for those alcoholics who themselves had independent depressions [9,81]. Similarly, independent major depressive episodes may be most likely to be observed in alcoholics who have relatives with such depressions [110–113].

However, it is important to remember that not all studies agree, and that groups of alcoholics with depressive syndromes are heterogeneous. A national AUDADIS-based survey concluded that past alcoholism may be

associated with an enhanced risk for major depressive disorders, even during apparent abstinence [114]. The relationship between alcoholism and depressive episodes in this study might reflect the presence of independent depressions among relatives of the alcoholics or the possible impact of stresses or lower social supports associated with rebuilding one's life following abstinence [13,80]. This study did not gather data from additional informants, or use blood or urine tests to corroborate the abstinence. On the other hand, a 1-year prospective follow-up of alcoholics using a SSAGA-like interview, along with data from additional informants and biological tests of abstinence, did not report higher rates of major depressive episodes, perhaps reflecting the smaller sample or the shorter time-frame of follow-up [116].

This discussion of the relationships between mood syndromes and substance use disorders would not be complete without a mention of two additional factors. While the acute phase of withdrawal from alcohol lasts 4 days or so, this is likely to be followed by a protracted abstinence syndrome that can last several months or more [117]. Here, while the alcoholic is not depressed all day every day (i.e. does not fulfill criteria for a major depressive episode), they are likely to experience insomnia, problems concentrating and irritability that improve with increasing time of abstinence. These mood-related conditions must be recognized by clinicians and treated, usually with education and cognitive behavioral approaches [16]. These are not, however, independent major depressive episodes. The second proviso is to emphasize the importance of evaluating whether what appears to be a substance-induced mood disorder actually clears with abstinence. It is at least theoretically possible that some individuals predisposed toward major depressive episodes might develop their syndromes in the context of the stresses associated with substance use disorders. As many as 15% of any group of individuals (including alcoholics) are likely to show major depressive episodes as a reflection of the usual prevalence of these mood disorders. Therefore, when symptoms consistent with a DSM-IV major depressive episode continue to occur daily and almost all day following 4 or more weeks of abstinence, the clinician should consider carefully the possibility that a major independent depressive episode is present, and treat the patient accordingly.

In summary, there is no easy or perfect answer regarding the manner in which major depressive episodes and alcohol dependence are related. Multiple factors, including substance-induced disorders, are likely to contribute to this comorbidity. None the less, the studies cited above document a high probability that substance-induced mood disorders contribute to the comorbidity observed.

THE CLINICAL RELEVANCE OF SUBSTANCE-INDUCED DISORDERS

There are three basic elements to this section. These include data indicating that substance-induced disorders are prevalent enough to be worth recognizing; they have a relatively unique clinical course compared to independent disorders; and their optimal treatments may be different than those most appropriate for independent conditions.

Substance-induced disorders are relatively common

Estimates of the prevalence of substance-induced psychiatric syndromes range from about zero [18] to 65% or more of some psychiatric conditions seen in alcoholics [14]. Lower estimates tend to come from large epidemiological studies, and higher rates when the SSAGA is used with close clinical oversight of interviewers. Substance-induced conditions are also likely to vary across psychiatric diagnoses and categories of drugs.

The life-time rate of temporary substance-induced psychoses in stimulant-dependent individuals may be at least 40%. The figures for cannabinoid-induced psychoses are more difficult to estimate, but the information presented earlier leaves little doubt that they exist.

Regarding the prevalence of other substance-induced conditions, it is helpful to review figures across studies using the same methods. I have chosen to emphasize data generated from the SSAGA or similar instruments with interviewer training and supervision similar to that used in COGA. Here, while 40% or more of alcoholics have histories of major depressive episodes, as many as 70% of these are substance-induced disorders [9,25,65–67]. Substance-induced conditions represented 20% of the panic disorders, 25% of social phobias, 40% of the obsessive-compulsive disorders and 50% of those with agoraphobia [9,26]. However, not all substances of abuse can induce all psychiatric pictures, and substance-induced conditions are observed less frequently in individuals dependent upon opioids and inhalants [9,16,118]. Therefore, in summary, most studies document substantial proportions of alcoholics and stimulant-dependent subjects have substance-induced conditions.

Substance-induced disorders offer useful information about prognosis

As reported above, the symptoms of most substance-induced conditions resemble closely those of the relevant independent psychiatric disorders [9,36,37]. However, 85% or more of substance-induced syndromes improve rapidly with abstinence, falling below the threshold for a diagnosis of an Axis I disorder within several days to a month. This clinical course is distinct from what would be expected with, for example, independent schizophrenia and major depressive episodes.

The required brevity of this review has not allowed for similar in-depth evaluations of anxiety conditions. However, stimulant-intoxication is associated with temporary panic attacks, generalized anxiety-like and phobic-like conditions in both the laboratory and clinical settings [27,59,119,120]. These, too, are temporary anxiety conditions that are very likely to clear with continued abstinence. Temporary substance-induced anxiety and mood syndromes have also been reported for hallucinogens and cannabinoids, and can be observed for other Axis I disorders (e.g. sleep, sexual dysfunction) [16,118]. Comorbidities of independent disorders also impact on outcomes. There is general agreement that comorbid substance dependence is associated with a more severe course of independent Axis I conditions, and that these long-term independent syndromes produce greater difficulty in treating the associated SUD [6, 52,121–123]. The course of the second disorder (e.g. major depression) may improve if the first disorder (e.g. an AUD) is in remission, and visa versa [124,125]. However, while some studies report that independent depressions in the context of substance dependence have a worse prognosis [105,106,126], others suggest a better than average outcome for the psychiatric condition [127–129]. It is likely that some of this diversity reflects the varying amounts of detail paid to separately evaluating substance-induced and independent disorders. Only carefully constructed studies will help to clarify the differences in the clinical course associated with comorbidities in substance-induced versus independent disorders, improve our level of knowledge about etiologies and lead to more effective treatments. These steps will be facilitated by the continued use of clearly defined substance-induced disorders in DSM-V.

Substance-induced disorders have unique treatments

The differences in short- and long-term prognoses between substance-induced and independent psychiatric disorders have several implications. First, regarding psychoses, reflecting the beneficial effects of antipsychotic medications for all forms of hallucinations and delusions, these drugs are likely to help control such symptoms in substance-induced psychotic conditions. However, such medications should be limited to the several days to a month it takes for substance-induced psychotic symptoms to disappear. Patients with long-term psychoses (e.g. schizophrenia) exacerbated by stimulants or alcohol are, on the other hand, likely to require long-term antipsychotic medications.

The conclusions are a little more complex regarding the optimal use of antidepressant medications in substance-dependent individuals. Even in classical independent major depressive episodes, non-pharmacological treatments help [130], and antidepressants often require 2–3 weeks to have an effect. In addition, there are few data to demonstrate whether antidepressants work equally well in depressive episodes induced by medications, medical disorders or substances of abuse. However, one might hypothesize these medications would be more effective than placebo in independent depressive episodes in substance-dependent patients and, reflecting the disappearance of depression with abstinence alone, not be much better than placebo for substance-induced disorders when patients abstain. Thus, the heterogeneity in clinical studies regarding steps used to identify substance-induced mood disorders may have contributed to differences in the reported usefulness of antidepressant drugs in patients with comorbid SUDs and depressive syndromes.

Studies from the 1980s indicated that alcoholics with comorbid depressions were not likely to respond to tricyclic antidepressants [131,132]. However, in a recent review of 14 controlled antidepressant trials in depressed patients with SUDs, half the papers reported a significant antidepressant response [103]. Regarding specific positive studies, a 12-week trial of 51 alcoholics with comorbid depression indicated that fluoxetine was associated with a greater improvement in depressive symptoms than placebo [133]. Perhaps these results reflect a several-weeks' period of abstinence before patients began active medications, a step that might have diminished the proportion of participants with substance-induced depressions. Another report used desipramine in 12 alcoholics who completed the trial and who had an onset of a depression following the development of alcoholism, comparing the results with 10 similar individuals treated with placebo [134]. Here, the medication was superior to placebo, but the group with active drug was small, subjects were abstinent between 1 and 12 weeks prior to entering the protocol and depressive symptoms were required to have lasted for at least 3 weeks in this 24-week trial. Other studies have evaluated the use of antidepressants in depressive episodes observed in opioid and stimulant-dependent individuals, with results not offering strong support for the use of medications [104,135].

Regarding the impact of antidepressants on drinking behaviors among alcoholics, a recent review indicated that three of nine controlled trials showed no difference between placebo and antidepressants, five a modest level of improvement with active treatment, and in one study the antidepressant was clearly superior to the placebo [103]. Another review of SSRIs indicated that in only one of six such investigations was the active drug clearly superior to placebo regarding drinking outcomes [136,137]. At the same time, manic-depressive alcoholics have been reported in one study to decrease drinking when treated with valproic acid [138]. Therefore, regarding antidepressant treatment of depressive episodes or

drinking in individuals with alcoholism, the answer may depend on how the question is asked. The variation in results across studies might reflect approaches that resulted in differences across trials in the number of individuals with temporary, substance-induced depressive episodes, cases where placebo and the passage of time might have been as effective as the antidepressants.

Space constraints do not allow for a more detailed review of the use of medications in the treatment of comorbid anxiety disorders in individuals with substance dependence. It is likely that a clear answer regarding the usefulness of medications will require investigations that evaluate data separately for individuals with substance-induced versus independent anxiety disorders.

SOME CONCLUSIONS

This analysis has focused on several questions relevant to the considerations required for the development of DSM-V. The material presented above indicates that substance-induced disorders exist, they are prevalent enough to contribute significantly to the rates of comorbidity between SUDs and psychiatric conditions, and these disorders have treatment implications. However, it is important to remember that substance-induced conditions explain only a subgroup of patients with comorbid SUDs and major psychiatric conditions. The current literature review underscores the heterogeneous nature of comorbidity, and raises the importance of identifying these subgroups of individuals with comorbid conditions in order to address both research and clinically based questions. This brief review has focused mainly on alcohol, cannabinoids and stimulants regarding psychoses and mood disorders, with brief mention of anxiety conditions, but the same general conclusions are likely to apply to some other drugs and psychiatric conditions.

This paper points toward several research priorities for comorbid conditions. There is a need to establish and standardize definitions and research methods relevant to studies of substance-induced disorders. Consensus is needed on a preferred definition of comorbidity along with clearer definitions of criterion items for SUDs (e.g. repeatedly), as well as greater consistency across studies on impairment or distress, clustering and remission. Research groups need to agree on the optimal methods to study comorbidities, possibly through a national cooperative study focusing on comorbidity, including substance-induced disorders. This could be patterned after national collaborations regarding depressive disorders and after COGA. In the absence of such approaches, the field is unlikely to be able to draw valid and generalizable conclusions regarding important aspects of comorbidity including data regarding the expected clinical course, treatments, etiologies and prevention of these syndromes.

In considering the definitions of comorbidity and substance-induced conditions for DSM-V, it is important to keep several issues in mind. The criteria should build upon data available to date, and not turn to major alterations of existing approaches unless supported by robust studies. Recognizing that the DSMs are primarily clinical manuals, it is also important that the criteria be relatively straightforward to encourage use by clinicians, insurers and administrators. Diagnoses must be flexible enough to be applicable across different categories of drugs, diverse psychiatric conditions and different ethnic and demographic groups, because the development of separate criteria for each drug and psychiatric diagnosis would result in an approach of such complexity as to jeopardize its general use.

In summary, this review has underscored the importance of comorbidity in substance use disorders, the heterogeneous and complex nature of these conditions, the relevance of substance-induced disorders and the difficulties inherent in establishing cause and effect or more generalizable treatment approaches based on the current literature. However, questions of the optimal approaches (note the emphasis on the plural) to types of comorbidities between substance use disorders and psychiatric conditions are important topics for future research as our field prepares for the development of DSM-V.

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