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Comorbid Alcohol, Cannabis, and Cocaine Use Disorders in Schizophrenia: Epidemiology, Consequences, Mechanisms, and Treatment

Abstract: There are high rates of substance use in patients diagnosed with schizophrenia. The objective of this review is to update clinicians about the epidemiology, consequences, assessment and treatment of comorbid substance use disorders and schizophrenia. Alcohol, cannabis and cocaine are among the most frequently abused substances in patients with schizophrenia. Substance abuse can negatively affect the expression and course of schizophrenia, for example by leading to a lower global level of functioning, increased hospitalizations, increased service utilization, and lower compliance with medication. Several models have been proposed to explain the high rates of comorbid substance use disorder in patients with schizophrenia including the self-medication and reward dysfunction hypotheses. There is little evidence to support the self-medication hypothesis. The reward dysfunction hypothesis is gaining support. The high rates and negative consequences warrant a thorough assessment of comorbid substance use disorders when treating patients with schizophrenia. The existing treatments are not particularly effective. Combination pharmacotherapy and behavioral strategies may be superior to either alone in the treatment of schizophrenia with comorbid substance use disorders. Due to the changing nature of DSM definitions of substance abuse and the drugs which are being abused, clinicians must strive to stay up to date on the latest findings related to co-occurring disorders among people with schizophrenia.

Author Information and CME Disclosure
The first three authors share first authorship.

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Dr. D'Souza reports the following: *Consultant:* Bristol Myers Squibb; *Research Funding awarded to Yale University:* Abbott, Pfizer, Lilly

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Introduction

Schizophrenia is a major psychiatric disorder that affects approximately 1% of the general population (1). The burden to individuals, their families, and society is enormous. Roughly half of people with schizophrenia have a co-occurring disorder (2). In this paper we review the problem of substance use disorders and schizophrenia. This review is focused on alcohol, cannabis, and cocaine, as there is some indication that these are among the most frequently-used substances among this population (3, 4). Additionally, a recent meta-analysis of substance abuse among people with schizophrenia determined that the majority of research on individual substances of abuse had been conducted on alcohol, cannabis, and cocaine (5). These three substances have unique

mechanisms of action, behavioral effects, and legal status, and there are undoubtedly substance-specific issues related to each of these three drugs. However, from a clinical perspective there are more similarities than differences; and the existing literature rarely differentiates these drugs adequately. Furthermore, patients with schizophrenia often use substances in combination. Hence, this review will mainly address common aspects of alcohol, cannabis, and cocaine; substance-specific issues will be addressed secondarily. Finally, nicotine and schizophrenia is a topic in itself and so is not discussed here.

WHAT ARE THE RATES OF SUBSTANCE ABUSE IN INDIVIDUALS DIAGNOSED WITH SCHIZOPHRENIA?

There is a high rate of substance abuse comorbidity among patients with schizophrenia. According to the National Survey on Drug Use and Health 2004-2005 report, the prevalence of alcohol and drug use disorders was about 23% in patients with serious mental illness in contrast to 8% in adults without serious mental illness (8) (Table 1). In both the Epidemiologic Catchment Area study (2) and National Comorbidity Survey (6), patients with schizophrenia had the highest lifetime rates of alcohol abuse (Lifetime prevalence =9.7%, OR=1.9) and drug abuse (Lifetime prevalence =14.6%, OR=6.9) compared with other mental illness. Rates of substance use disorders (SUDs) in patients with schizophrenia in published studies vary from 7% (9) to 59.8% (10). Despite differing methodologies, the overwhelming majority of studies have indicated that SUDs are more prevalent in schizophrenia than in the general population. The pattern of use, abuse, and dependence of different substances in schizophrenia as compared with mood disorders and the general population is detailed in Table 2.

Interestingly, there may be a temporal trend in the rates and pattern of substance-abuse among patients with schizophrenia. Studies suggest that the most commonly abused substances in the 1970-80s were (in decreasing order of rates of abuse) tobacco, amphetamines and cocaine, hallucinogens and cannabis, and alcohol (reviewed in (17)). While the rates of lifetime abuse/dependence of alcohol and stimulants increased twofold from the 1970s to the 1990s, the rates of hallucinogen abuse/dependence decreased by half, and the rates of cannabis abuse/dependence did not change. The pattern of lifetime substance dependence among patients with schizophrenia in the 1990s was (in decreasing order of rates of abuse) alcohol (46.9%), cannabis (28.3%), amphetamines (9.3%), benzodiazepines (6.2%), opioids (prescription and nonprescription) (4.7%), hallucinogens (4.1%), solvents and anticholinergics (3.6%), and cocaine (1.5%) (18). While an analysis of the NIMH CATIE trial showed that patients with schizophrenia and comorbid substance-use disorder used (in decreasing order of rates of abuse) alcohol (87%), cannabis (44%), and cocaine (36%) (19), another study showed that the most commonly abused substances were (in decreasing order of rates of abuse) alcohol (57%), cannabis (48%), hallucinogens (20%), cocaine (14%), stimulants (27%), sedatives (13%), and opioids (9%). Opioid abuse occurs at relatively low rates in schizophrenia patients probably because the level of social functioning necessary to carry out life as an opioid addict is often higher than that which a patient with schizophrenia is typically able to maintain. There was also an increased rate of polydrug use (16%) in this population (20). Of course, in the absence of any longitudinal study that has tracked SUDs in people with schizophrenia the proposed temporal trends can only be inferred from cross-sectional studies, which may not account for methodological and/or geographic variability.

WHAT ARE THE CONSEQUENCES OF SUBSTANCE ABUSE/DEPENDENCE ON THE EXPRESSION AND COURSE OF SCHIZOPHRENIA?

Comorbid substance use negatively impacts the course and expression of schizophrenia. For example, comorbid substance use in schizophrenia has been associated with higher scores on positive symptoms, negative symptoms and general psychopathology (21, 22); service utilization (23); higher rates of noncompliance with medication (22); and higher depressive symptoms (22).

A 15-year longitudinal study found that patients with dual diagnosis of schizophrenia and substance-use disorders, including alcohol-use disorders, had higher rates of hospitalization, poor insight, homelessness, violent offending, and increased risk of death (24). Overall, alcohol use disorders (AUDs) are associated with poor adjustment and poor outcome in almost every domain of functioning (22, 25–27). Patients with comorbid alcohol use disorder are also more cognitively impaired than those with a single diagnosis of either schizophrenia or AUDs on measures of attention, global cognitive functioning, verbal memory, and reasoning/problem solving (21, 28).

Of note, even though comorbid alcohol and substance use disorders have negative consequences for patients with schizophrenia, motivation for reduction of substance use in this population is usually low (29, 30). Finally, patients with schizophrenia with active psychotic symptoms may be more likely to abuse alcohol than those without psychotic symptoms (31); this is problematic in that patients who are psychotic might be more

Table 1. Prevalence of Alcohol and Drug Use Disorders Among Psychiatric Disorders

Diagnosis	Alcohol abuse				Alcohol dependence			
National Comorbidity Survey[1]	**1–yr (%)**	**OR**	**LT (%)**	**OR**	**1–yr (%)**	**OR**	**LT (%)**	**OR**
Mood disorders	2.8	1.1	9.2	1.0	11.8	3.6*	26.4	2.8*
Major depressive disorder	2.8	1.1	9.1	1.0	12.1	3.7*	26.4	2.7*
Bipolar disorder	1.8	0.7	3.1	0.3	22.4	6.3*	61.1	9.7*
Anxiety disorders	3.8	1.7	10.4	1.2	8.5	2.6*	21.4	2.1*
GAD	1.1	0.4	8.4	0.9	16.2	4.6*	29.8	2.8*
Panic disorder	1.4	0.5	9.6	1.0	7.4	1.7	24.4	2.0*
PTSD	3.7	1.5	6.5	0.7*	8.8	2.2*	28.1	2.6*
Epidemiologic Catchment Area[2] study	1–yr (%)	OR	LT (%)	OR	1–yr (%)	OR	LT (%)	OR
Schizophrenia	—	—	9.7	1.9	—	—	24.0	3.8+
NESARC[3]	1–yr (%)	OR	LT (%)	OR	1–yr (%)	OR	LT (%)	OR
Schizophrenia	—	—	16.6	0.88	—	—	38.2	4.4*

OR =Odds Ratio.
* Odds ratio was significantly different from 1 at <0.05.
+ Odds ratio was significantly different from 1 at <0.001. The odds ratio represents the increased chance or comorbid psychiatric and substance use disorder (e.g. a person with schizophrenia is 6.9 times more likely to also have comorbid drug abuse compared with a person without schizophrenia). 1–yr rate (%) is the percentage of people who met the criteria for the disorder during the year prior to the survey. LT(%)= Lifetime rate (%) is the percentage of people who met the criteria for the disorder at any time in their lifetime. SOURCES: [1]Kessler et al. 1996 (6). [2]Regier et al. 1990 (2). [3]McMillan et al, 2009 (7)

vulnerable to the negative effects of substance use in general.

In patients recently diagnosed or at high risk for schizophrenia, cannabis use resulted in increased anxiety, depression, and suspicion soon after cannabis use, but lowered depression in some high risk subjects (32). In recently diagnosed schizophrenia patients, cannabis resulted in increased hallucinations and confusion. Both patient groups reported long-term cannabis use resulted in greater rates of depression, less control over thoughts, and more social problems. Contrary to the effect of cannabis on the positive and negative symptoms of psychosis, comorbid cannabis use disorder is associated with improved cognitive performance on tests of visual memory, working memory, and executive functioning both in chronic schizophrenia (33, 34) and first-episode schizophrenia (35). Although counterintuitive, it is likely that patients with cannabis-use disorders have better premorbid cognitive functioning because of the cognitive demands involved in procuring an "illegal" substance, abusing it, and being able to evade the legal system. This may explain the better performance despite a deterioration in cognitive functioning that occurs as a result of the pathological processes of schizophrenia. Also, about 37% of recent-onset patients with schizophrenia reported that their very first psychotic symptoms occurred during cannabis intoxication.

It is interesting to note that in some recent studies, patients with schizophrenia also differ from the general population in terms of the type of cannabis that is abused (36). People with schizophrenia were more likely to use cannabis with high delta-9-tetrahydrocannabinol (THC) and low cannabidiol (CBD) content, (sinsemilla which contains 15% THC and less than 1.5% CBD being a case in point) while healthy controls were more likely to use cannabis with a more balanced concentration of cannabinoids (e.g. hash which contains 3.4% each of THC and CBD).

Studies comparing clinical symptoms in schizophrenia patients with and without a history of cocaine use have produced mixed results including lower negative symptoms, more paranoid symptoms, more hostility, more depression, higher levels of both recent positive and negative symptoms, or no differences in positive or negative symptoms in cocaine using patients (37–41). A history of cocaine abuse has been associated with more frequent hospitalizations compared with people with schizophrenia who use other substances (40). The CATIE study found that schizophrenia patients who used cocaine had lower psychosocial functioning, especially in relation to work, school, or homemaking compared with those who used other substances and to those without a SUD (11).

The effects of cocaine use on cognitive test performance in schizophrenia patients are unclear. Some

Table 1. Continued

Drug abuse				Drug dependence				Any Substance Abuse/ Dependence			
1–yr (%)	OR	LT (%)	OR	1–yr (%)	OR	LT (%)	OR	1–yr (%)	OR	LT (%)	OR
1.1	1.4	6.5	1.7*	5.2	3.9*	15.6	3.0*	18.3	3.0*	41.2	2.3*
1.2	1.6	6.6	1.7*	5.0	3.6*	15.4	2.8*	18.4	3.0*	41.4	2.3*
1.8	2.3	5.4	1.2*	12.9	8.2*	40.7	8.4*	37.1	6.7*	71.0	6.8*
1.0	1.3	5.5	1.4*	4.3	3.6*	14.6	3.3*	15.2	2.5*	37.8	2.1*
1.3	1.7	6.3	1.5	3.2	1.8	21.9	3.8*	21.0	3.1*	42.3	2.1*
0.2	0.2	6.6	1.6	7.4	4.7*	22.5	3.8*	16.0	2.2*	41.2	2.0*
1.1	1.5	6.8	1.6*	6.5	4.2*	21.9	4.0*	17.7	2.5*	45.2	2.5*
1–yr (%)	OR	LT (%)	OR	1–yr (%)	OR	LT (%)	OR	1–yr (%)	OR	LT (%)	OR
—	—	14.6	6.9+	—	—	12.9	4.2+	—	—	47.0	4.6+
1–yr (%)	OR	LT (%)	OR	1–yr (%)	OR	LT (%)	OR	1–yr (%)	OR	LT (%)	OR
—	—	27.6	3.76*	—	—	18.9	8.32*	—	—	—	—

studies report that, cocaine using schizophrenia patients have greater impairments on selected cognitive tests, less impairments or no differences (41–46). Cocaine-dependent schizophrenia patients who were abstinent for at least 72 hours outperformed nondependent schizophrenics on tasks involving motor speed and executive functions (47). Furthermore, after about 2 weeks of abstinence from cocaine, there appear to be no differences in cognitive test performance between schizophrenia patients with and without cocaine use (46).

Remission rates were lower for cocaine compared with alcohol and other substances (40) suggesting that schizophrenia patients may have greater difficulty quitting cocaine use. Consistent with this, in a longitudinal study of schizophrenia outpatients, while the use of alcohol, cannabis, and other substances remained stable, cocaine use increased over time (48).

How successful are schizophrenia patients at achieving and maintaining abstinence?

There is a paucity of data on the success rate of patients with schizophrenia and comorbid SUDs at achieving and/or maintaining abstinence. Furthermore little is known as to how this rate compares with patients with SUDs who do not have schizophrenia. A study using data from the NIMH-ECA study showed that remission rates of SUDs in schizophrenia patients were 31% for alcohol and 50% for other drugs (49). In contrast, 61% of schizophrenia patients with comorbid AUDs who received assertive community treatment achieved and maintained remission (50). Finally, in a cohort of schizophrenia patients who were engaged in a work rehabilitation program, 71% of alcohol users, 53% of cocaine users, and 79% of all other substance users remained abstinent after 12 months (40).

There are very few studies comparing abstinence outcomes of psychotic and nonpsychotic patients. A multisite study of outpatient veterans found no significant differences in abstinence rates between patients with SUDs with and without comorbid psychotic disorders (51). Another smaller study of patients who attended a 4-month integrated dual-diagnosis inpatient program found that that personality disorder patients showed a greater reduction in their alcohol but not other substance use compared to psychotic disorder patients after a 1 year follow-up (52). However, a longer (5-year follow-up) study showed that a diagnosis of schizoaffective disorder predicted longer times to achieve remission (defined as at least 6 months of abstinence prior to the assessment) compared with nonpsychotic affective disorders (53).

Reasons for the high rates of substance abuse and dependence in schizophrenia

The reasons for the high rates of comorbid substance abuse and dependence SUD in schizophrenia are not well understood. There may be explanations that are common to all substances, as well as explanations that might be substance specific. While it is out of the scope of this article to review all the hypotheses, we now focus on some leading

Table 2. Pattern of Use, Abuse and Dependence in Schizophrenia, Mood Disorders and General Population

	Schizophrenia			Mood Disorder			General Adult Population (NSUDH) (SAMHSA 2010)	
	Rates of use	Rates of DSM-IV Abuse or Dependence	Rates of DSM-IV Dependence	Rates of use	Rates of DSM-IV Abuse or Dependence	Rates of DSM-IV Dependence	Rate of Abuse or Dependence in 2010 (18-25yrs/ >26yrs)	Rates by DSM-IV Dependence in 2010 (18-25yrs/ >26yrs)
Nicotine	60%–90%[6-8]	—	45.3%	54.8%–57.4%	51.2%	33%	28%[1] / 36.8%[2]	14.3% /13.9%
Alcohol	85.9%–92.8%	32.8%	43.1%–65%	88.5%–90.1%	30%–69%[4]	28.8%[4]	15.6% / 5.9%	6.5% /2.9%
Cannabis	38.6%–51.8%	7.9%	50.8%	32.7%–35.1%	12.7%[4]	7.0%[4]	7.8% / 1.7%	3.7% / 0.5%
Cocaine	14.9%–25.6%	7.7%	36%[3]	11.0%–12.8%	4.2%[4]	7.0%[4]	0.7% / 0.4%	0.4% / 0.3%
Opioids	12.4%–22.8%	1.1%	10.2%	9.7%–11.4%	2.8%[4]	2.8%[4]	0.1%	—
Heroin	0.8%–4.3%	1.1%	2.2%	0.5%–1.0%	0.3%	0.01%	0.3% / 0.1%	0.3% / 0.1%
Hallucinogens	16.2%–28.5%	3.4%	13.4%	10.7%–12.5%	2.8%[4]	0.0%[4]	0.6% / 0.0%	0.2% / 0.0%
Stimulants (including methamphetamine)	11.8%–21.3%	2.7%	9.5%	9.6%–11.2%	2.8%[4]	2.8%[4]	0.4% / 0.1%	0.3% / 0.1%

[1] Rates of abuse/dependence in 18 yr olds
[2] Rates of abuse/ dependence in 26-29 year olds. Also represents highest rate in any age group.
[3] CATIE-NIMH data (11).
[4] Chengappa et al 2000 (12).
[6] de Leon et al, 2005 (13).
[7] Dervaux et al, 2008 (14).
[8] Ziedonis et al, 2003 (15).
Synthesized from NESARC data and Volkow, 2009 (16).

hypotheses that have been proposed to explain the association between SUDs and schizophrenia (54, 55): 1) Self-medication, 2) Differential emotional valence, 3) Reward dysfunction, and 4) Genetics.

THE 'SELF-MEDICATION' HYPOTHESIS

A hypothesis that has significantly influenced clinical practice, is that people with schizophrenia use substances to "self-medicate" psychiatric symptoms and/or side effects (56). Surveys have identified some common themes as to why schizophrenia patients use substances including 1) to cope with negative feeling states or to relax (18, 57–64), 2) to enhance positive mood ("feel good") or achieve intoxication ("get high") (18, 57), 3) as a social lubricant ("something to do with friends", "to go along with the group", and "to face people better") (18, 65), and 4) to relieve medication side-effects (17) or symptoms (66). Many of the reasons that schizophrenia patients state for using alcohol and cannabis do not seem very different from those given by the general population.

However, retrospective self-report data are subject to distortion. Individuals who misuse substances typically use denial and rationalization to justify their use. In addition, several substances e.g. alcohol and cannabis alter perception and have amnestic effects that may influence the interpretation of events and therefore interfere with the accurate recall of effects. Substances are often used in combination so it is difficult to attribute consequences solely to one substance in naturalistic studies. Finally, it is possible that the positive and negative effects of substances may be dose-related, and dose-response relationships are almost impossible to assess in naturalistic studies because dose is seldom measured accurately. Some limitations of self-report literature can be addressed through experimental studies as well as experience sampling.

D'Souza et al. compared the effects of alcohol on schizophrenia patients and controls in a randomized, double-blind, placebo-controlled, counter-balanced 3 test day laboratory study (67). Standard alcohol drinks in a scheduled design were administered to produce blood alcohol levels of 0, 0.02–0.04 mg%, or 0.06–0.08 %. Relative to healthy subjects, subjects with schizophrenia reported greater euphoria and stimulatory effects in response to alcohol. Alcohol produced small transient increases in positive psychotic symptoms and perceptual alterations without affecting negative symptoms. Alcohol also impaired several aspects of cognitive test performance. The absence of 'beneficial' effects of alcohol does not support a self-medication

hypothesis of alcohol use in schizophrenia. Schizophrenia patients also showed increased euphoric and stimulatory responses to alcohol raising the possibility that these exaggerated positive responses to alcohol doses may contribute to the increased risk for AUDs associated with schizophrenia.

D'Souza et al. also studied the dose-related behavioral, cognitive, motor and endocrine effects of Δ-9-THC in stable, antipsychotic-treated schizophrenia patients (68). The 3 day study was double-blind, randomized, and placebo-controlled and Δ-9-THC was administered intravenously. Δ-9-THC transiently increased positive, negative and general schizophrenia symptoms, perceptual alterations, attention, memory, akathisia, rigidity, and dyskinesia. Δ-9-THC is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia. These data challenge the "self-medication" hypothesis of cannabis use/misuse in schizophrenia. However, this study had limited ecological validity; subjects were given Δ-9-THC and not cannabis, smoking cannabis is different from intravenous Δ-9-THC, subjects were unable to titrate the dose, and the setting was very different from the recreational setting.

Recently, Henquet et al. (69) conducted a more ecological valid study using the Experience Sampling Method (ESM) (70, 71). Unlike the laboratory study by D'Souza et al., in this study subjects smoked cannabis, and did so in a familiar set and setting. Subjects received a digital wristwatch, and a paper-and-pen ESM booklet. Twelve times a day on six consecutive days, the watch beeped randomly once in each 90-minute time block between 7:30 a.m. and 12:30 p.m. After each beep, the subject completed a 7-point Likert scale on affect, thoughts, symptom severity, and activity at the moment of the beep. This design allowed the investigators to establish a relationship between symptoms and the use of cannabis (was cannabis use preceded by an increase in symptoms, and conversely was cannabis use followed by a decrease in symptoms?). Neither positive nor negative affect predicted cannabis use at the next sampling point. Similarly, no associations were found between delusions or hallucinations and subsequent cannabis use. Cannabis acutely induced hallucinatory experiences and decreases in negative affect were observed after cannabis use. The authors determined that cannabis may have biphasic effects on mood and psychotic symptoms, with increases in positive affect observed immediately after cannabis use, but not hours later. The fact that propsychotic effects of cannabis did not occur immediately shows that cannabis may have immediate positive effects on mood followed by later negative effects on psychotic symptoms. The authors concluded that this delay between immediate reward and negative consequences rather than self-medication might explain why schizophrenia patients continue to use cannabis.

Collectively, the controlled data do not support the version of the self-medication hypothesis according to which schizophrenia patient use substances to alleviate symptoms and side-effects. More likely, schizophrenia patients might use substances to alleviate dysphoria associated with several causes (e.g. anxiety, depression, boredom, and loneliness) (54), the same reasons why people without schizophrenia use substances.

INCREASED POSITIVE AND DECREASED NEGATIVE VALENCE OF SUBSTANCES IN SCHIZOPHRENIA PATIENTS

As discussed above, schizophrenia patients may have greater vulnerability to the euphoric effects of substances, as shown with alcohol (67) and greater difficulty anticipating the delayed negative consequences of substances, as shown with cannabis (69). This is consistent with the large body of literature showing that individuals at high risk for AUDs are more sensitive to the stimulating effects ("positive") of alcohol and less sensitive to its sedative effects ("negative") and similarly, alcohol is more likely to be consumed if it is experienced as strongly rewarding and/or if it causes few negative effects (72–74). In fact, schizophrenia patients respond to reward stimuli in a manner similar to patients with drug abuse or dependence, and also similarly to patients with damage to their ventromedial prefrontal cortex (75–78), overvaluing drug rewards while devaluing the potential negative consequences of drug use. The combination of a greater vulnerability to the immediate "positive" effects of substances combined with greater difficulty anticipating the delayed "negative" consequences of substances may explain why schizophrenia patient are more prone to substance abuse/dependence.

REWARD DYSFUNCTION HYPOTHESIS

The pathophysiology of schizophrenia, the rewarding effects of substances, and the mechanism of action of all antipsychotic medications involve brain dopamine systems. The positive symptoms of schizophrenia are believed to be related to increased mesolimbic dopaminergic activity, while negative symptoms and cognitive deficits are related to reduced mesocortical dopaminergic activity. The mesolimbic dopamine (DA) pathway has also been implicated in the rewarding mechanism for all drugs of abuse. Furthermore, all existing antipsychotic

drugs block dopamine D2 receptors in dopaminergic pathways. Several groups have suggested that a dysfunction in the neural circuits mediating reward and reinforcement may predispose people with schizophrenia to substance abuse (79, 80). Green et al., proposed that the dysregulated dopamine-mediated mesocorticolimbic brain pathways that are believed to be involved in the pathophysiology of schizophrenia are also the basis of a reward circuit deficit in these patients (79), and that the use of substances transiently reduces this deficit but at the same time worsens the course and expression of schizophrenia (79, 81). In turn, Krystal et al. suggested that alterations in the hippocampal formation and frontal cortex facilitate the reinforcing effects of drug reward and decrease the inhibition of drug-seeking behavior, increasing the likeability of developing substance abuse disorder (82).

Sensation seeking and novelty seeking are believed to be risk factors for substance abuse (83). Concordantly, some studies have found that substance-abusing patients with schizophrenia show elevated levels of novelty seeking (84, 85) and sensation seeking (86, 87) versus patients with schizophrenia without substance-use disorders.

SHARED GENETIC BASIS FOR SUBSTANCE ABUSE DISORDERS AND SCHIZOPHRENIA

One of the possible explanations for the high rates of SUDs in schizophrenia patients may be a shared genetic risk for the two disorders. For example, polymorphisms of the D2 dopamine receptor gene (D2R2) influences susceptibility to schizophrenia (88) and variants of this gene have also been related to the aspects of alcohol dependence (89, 90).

ASSESSMENT

The presence of comorbid substance use poses a great challenge to the management of schizophrenia, as it can be frequently under-diagnosed and inadequately treated. Since the rates of comorbidity of substance use disorders are high in schizophrenia patients and negatively impact the course and expression of the disorder, assessment and treatment of comorbid substance abuse can have a positive impact on the course and expression of schizophrenia. There is relatively little information specifically about the assessment and treatment of comorbid SUDs and schizophrenia. This reflects the relative paucity of research in this area despite the important clinical implications of comorbid SUDs on the course and expression of schizophrenia. The most likely reason for this lack of research is that studying schizophrenia patients with comorbid SUDs presents significant challenges. Most of what is presented below is the assessment and treatment of SUDs in general. When available, information specifically about the assessment and treatment of comorbid SUDS and schizophrenia is highlighted.

HISTORY

There is no substitute to taking a careful history of substance use in all patients with schizophrenia, given that the rates of comorbid substance abuse are so high in this group. The more it becomes part of routine evaluation, the more likely that it will become to be expected by patients and clinicians as part of the evaluation process. Assessment of patients should always include comprehensive, nonjudgmental evaluation of substance use history. Information should be gathered from the patient as well as collaterals including the patient's friends, family, and other treatment providers within a motivational-interviewing framework (91). The presence of behaviors suggestive of substance use such as missed appointments, noncompliance/irregular compliance with medication, financial or legal problems, homelessness, frequent hospitalizations, transient exacerbation of psychosis on a previously stable dose of medication, and poorly controlled comorbid medical conditions like hypertension and diabetes should alert the psychiatrist to this possibility and encourage a more detailed assessment. The assessment should also include an evaluation of risk factors for violence and suicidality; the presence of personality disorders; the degree of motivation for substance abuse treatment; and high risk behaviors that increase the risk of HIV, Hepatitis B and C, and cardiovascular disease.

SCREENING TOOLS

A number of tools have been developed to screen subjects for substance use; the WHO's Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) (92) being one of the more recent tools. Although traditionally screening tests used in general population are found to be insensitive in persons with schizophrenia, some scales such as, the Alcohol Use Disorder Identification Test (AUDIT) (93), the Michigan Alcoholism Screening Test (MAST) (94), and the Drug Abuse Screening Test (DAST) (95) have demonstrated reliability and validity. Furthermore, there are scales which have been specifically devised for patients with severe mental illness. These include the Dartmouth Assessment of Lifestyle Instrument for Screening (96), the Alcohol Use Scale and the Drug Use Scale (97), and the Substance Abuse Treatment Scale (SATS) (98). The SATS is an 8-point scale that measures motivation for substance abuse treatment in patients

with severe mental illness and indicates whether the patient is in the stage of 'engagement', 'persuasion', 'active treatment' or 'relapse prevention'. The Time-Line Followback approach, which has been adapted for patients with severe mental illness (99) could be used to obtain a detailed account of substance use over the past 6 months. Each tool has strengths as well as limitations and there is no widely-agreed upon "gold standard" (100).

PHYSICAL EXAMINATION

A thorough physical examination should focus on abnormal vital signs, stigmata of liver disease such as jaundice, hepatomegaly, parotid enlargement, spider naevi, palmar erythema, ascites, gynecomastia and caput medusa indicative of alcoholic liver disease or viral hepatitis; papillary constriction/dilatation, needle puncture marks, and vein track marks resulting from intravenous drug administration, ecchymoses, thrombophlebitis, focal burns of varying ages on lips, mucosa, and opposing surfaces of fingers (palmar surface of thumb and index finger), and calluses on the palmar surface of the thumb resulting from frequent use of the lighter to heat cocaine crystals. Palatal perforation and ulceration of the nasal septum may indicate cocaine use disorder. Lacrimation, rhinorrhoea, piloerection and yawning indicate opioid withdrawal, and conjunctival hyperemia may suggest the presence of cannabis use. Additional signs include cheilosis seen in chronic amphetamine and opioid dependence and "glue sniffers rash" seen as a contact dermatitis around the nose, mouth and hands. The physical examination should also assess nutritional status, presence of vitamin deficiencies, weight, BMI, waist circumference, and cardiovascular risk.

LABORATORY TESTS

Laboratory tests may indicate the regularity and severity of substance use. These include breathalyzer; urine toxicology; and analysis of hair, nail, sweat and saliva. The breathalyzer is a sensitive and inexpensive test to detect recent alcohol use but its utility is limited based on quantity of alcohol consumed, time window of assessment, and individual variation. The urine toxicology detects metabolites of substances of abuse and can quickly screen for multiple substances with one test. The metabolites of substances however only remain in the body for a limited period of time and hence the test has a relatively narrow detection period (e.g. 6–24 hours for alcohol, 2–5 days for cocaine, 2-7 days for cannabis; although can be >30 days with chronic severe dependence, 1–7 days for amphetamine). The tests also yield false negatives and there are many products available over the internet that claim to be able to beat the drug test. While the window of detection with the analysis of saliva is comparable to that with urine, the window of detection with hair and nails is longer at 90 days and 6 months, respectively, for some substances.

Serum biomarkers are useful in estimating the severity of alcohol use. Increased levels of the glycoprotein carbohydrate deficient transferrin (CDT), gamma glutamyltransferase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (AST) indicate recent alcohol use. CDT and GGT are particularly sensitive to alcohol use. The mean corpuscular volume of red blood cells is also increased with increasing alcohol use.

The evaluation of patients with schizophrenia and comorbid SUDs should include an evaluation for other comorbid disorders. Personality disorders, depression, and anxiety disorders are frequent comorbidities and may require treatment with SSRIs. A cognitive-behavioral analysis of the causes, cues, and triggers of substance use helps to identify treatable or modifiable factors (91). If substance use is used as a method to overcome side-effects related to antipsychotic use, such as akathisia, dysphoria, and extrapyramidal symptoms, titrating the dose of antipsychotic and anticholinergic drugs or switching to another antipsychotic such as clozapine may be reasonable alternatives. Finally, assessing motivation to use is important when considering treatment options.

Recommendations to clinicians:

- Always consider the possibility of comorbid substance-use disorder in every patient.
- Take an accurate and thorough history.
- Watch for behaviors and physical symptoms indicative of substance use.
- Use laboratory tests and third-party information to corroborate the history and assess severity.
- Assess for other comorbid affective, anxiety and personality disorders.

TREATMENT AND OUTCOMES

Addressing comorbidity of SUD in schizophrenia has important clinical implications for both the prevention and treatment of these two disorders and also for decreasing morbidity and mortality. Despite the high prevalence of comorbid SUD among people with schizophrenia, the negative outcomes associated with the two, and the associated healthcare costs there is a considerable paucity of rigorously conducted randomized controlled treatment trials.

Furthermore, there is a need to integrate the treatments for schizophrenia and SUDs, which are sometimes delivered independent of each other. As reviewed by Green et al., the lack of an integrated approach leads to inconsistent treatment, and occasionally iatrogenic side effects (101). The success of any treatment approach depends on the establishment of a collaborative, therapeutic alliance with the patient (102). This is hence a necessary first step in treatment.

BEHAVIORAL TREATMENTS

While there is considerable research that has been conducted on behavioral interventions for SUDs, whether these approaches are just as applicable or effective in dually diagnosed patients is not clear. Existing behavioral treatments for SUDs may not be suitable for schizophrenia patients with SUDs. For example, patients with schizophrenia may not be able to access the support given by Alcoholics Anonymous (AA) members (103) due to cognitive symptoms and limited social skills. However, the 12-Step approach has been found to be effective for reducing substance use and mental illness through the mediational role of social support and improvement in self-efficacy (104). Furthermore, schizophrenia patients may not be able to tolerate the confrontational style of certain kinds of behavioral interventions.

The Schizophrenia Patient Outcomes Research Team (PORT) guidelines (2009) recommend psychosocial interventions to be offered to patients with schizophrenia and comorbid SUDs (105). The key elements of treatment for people with schizophrenia and co-occurring SUD include motivational enhancement (ME) and behavioral strategies that focus on engagement in treatment, coping skills training, relapse prevention training, and its delivery in a service model that is integrated with mental health care. Both brief (1–6 meetings) and more extended (10 or more meetings) interventions have been found to be helpful in reducing substance use and improving psychiatric symptoms and functioning.

Motivational interviewing can facilitate establishing a therapeutic alliance, a key element in retaining patients in treatment. Green et al. recommend that clinicians should strive to suspend judgment of patients with co-occurring disorders in order to increase therapeutic rapport (106). Contingency management (CM) strategies that involve the use of a tangible reinforcer, such as contingent monetary reinforcement (107) or voucher-based contingent reinforcement (108, 109) following observable evidence of abstinence has been found to be useful in reducing use of cannabis, cocaine and cigarette smoking.

PHARMACOLOGICAL APPROACHES

There are few studies that have tested pharmacological treatments for schizophrenia patients with comorbid SUDs (110–113). Data, mainly based on open studies or case series, suggest superior efficacy for second generation antipsychotics (SGAs) in the improvement of distinct psychopathological symptoms and reduction of craving and substance use compared with orally administered first generation antipsychotics (FGAs) (101, 114, 115). Most of the published literature is based on the efficacy of risperidone and olanzapine (reviewed in (114)). A six week double-blind study comparing olanzapine and haloperidol in cocaine dependent schizophrenia patients found a significant reduction in the craving measures and fewer positive urine toxicology screens in the olanzapine group (116). However, in a twenty six week prospective, randomized, parallel group design comparing olanzapine and haloperidol in cocaine dependent schizophrenia patients, there were no differences in the proportion of positive drug screens between groups but interestingly, craving for cocaine was significantly lower in the haloperidol group (117). Long-acting injectable SGAs may also be more effective than long-acting injectable FGAs (118). Substantial literature is available on the utility of clozapine in comorbid alcohol-, cannabis-, and cocaine-use disorders (reviewed in (110)). The superior efficacy of clozapine in decreasing rates of substance use (119) which also correlates with clinical improvement (119), particularly in negative symptoms (120), and in preventing relapses (121) makes clozapine the antipsychotic of choice in patients with schizophrenia and comorbid substance use disorder.

Treatment with the opioid antagonist, naltrexone added on to antipsychotic treatment has been shown to decrease measures of alcohol use and craving, without worsening in psychotic symptoms (122–124). While the efficacy of add-on acamprosate in reducing alcohol use has not been shown, it can be administered safely to schizophrenia patients with AUD (113, 125). A few studies with add-on disulfiram suggest that it may reduce alcohol use in schizophrenia patients with AUD (reviewed by Wobrock and Soyka [126]). Of note, despite the theoretical possibility of worsening psychosis, this has not been observed in clinical trials with disulfiram. Nevertheless, in prescribing disulfiram to schizophrenia patients with comorbid AUD, it will be prudent to ensure that the subject fully understands the possibility of an Antabuse reaction, and to document this.

Tricyclic antidepressants and mood stabilizers may have a role in cases where patients use substances to

self-medicate depression or antipsychotic-induced dysphoria. Desipramine, imipramine, and lamotrigine given adjunctive to antipsychotic maintenance therapy showed some efficacy in reducing substance use and craving for cocaine and alcohol, respectively (127–129).

As reviewed above, there are few proven pharmacological options for the treatment of comorbid SUDS in schizophrenia patients. Clozapine might be the most effective, but not all patients might be willing to try clozapine or it might not be logistically possible to offer all eligible patients clozapine. Hence, there is a continuing need for new treatments for comorbid SUDS in schizophrenia patients.

COMBINATION APPROACHES

There are few studies that have tested the combination of pharmacological and behavioral interventions in the treatment of schizophrenia patients with comorbid SUDs. Haddock et al. compared routine care of medication and case management with integrated treatment that additionally included cognitive behavioral therapy (CBT) plus motivational interviewing in 36 patients with comorbid schizophrenia and substance use disorders (130). After 18 months, patients in the treatment group had higher GAF scores and fewer negative symptoms. However, there were no differences in self-reported substance use. Easton et al. (2007) compared 12-Step participation to integrated treatment for substance abuse and domestic violence and found similar effects, although there was some indication that the integrated treatment was superior (131).

As evidenced in a Cochrane review, integrated psychosocial treatment programs that include intensive outpatient treatments, case management services, and behavioral therapies such as CM are likely to be most effective for treatment of severe comorbid conditions (132). While not ideal and more as a last resort, more invasive and paternalistic approaches have to be considered including conservatorship and/or collaborating with the judicial system to facilitate abstinence and treatment compliance (133).

Recommendations to clinicians:

- Establish a collaborative, therapeutic alliance with the patient.
- Consider second generation antipsychotics, long-acting injectable SGAs, and clozapine as first line pharmacotherapy.
- Combine motivational enhancement, cognitive-behavioral interventions, and social support strategies along with regular drug-testing and contingency management.
- Consider adjunctive anticraving agents, antidepressants, and opioid antagonists.

FUTURE DIRECTIONS

The high rates of comorbidity of substance abuse among patients with schizophrenia can be interpreted in a number of ways. On the one hand, the high rates of comorbidity may represent 'true comorbidity' (i.e. co-occurrence of etiologically independent disorders), while on the other hand it is also likely that the comorbidity is a spurious epiphenomenon resulting from the use of an arbitrary, rule-based, classificatory system such as the DSM. With refinements to syndromal definitions, combined with greater understanding of the genetic architecture of schizophrenia and substance use disorders, and of how phenotypes map onto brain dysfunction, the hope is that the classificatory system of the future will be able to accurately demarcate etiologically distinct disorders.

The current classification of substance use disorders relies on the DSM-IV-TR definitions. DSM-5, scheduled for publication in spring 2013, will likely change the categories and definitions of categories for almost all items in the substance use section. There are several proposed changes, all or none of which may make it into the final document. It is likely that the "abuse" and "dependence" categories will be merged into one overarching category of substance misuse (134). There is some evidence that differentiating between patients who "merely" abuse a drug and those who are dependent upon it is not a clinically useful distinction. These and other changes will undoubtedly impact the classification and assessment of patients, irrespective of treatment. Another change will be the inclusion of cannabis withdrawal as a new clinical entity. Cannabis withdrawal consists of physical symptoms, insomnia, and dysphoric mood (135). It is important for clinicians to monitor patients for symptoms not only of cannabis use and dependence but also for withdrawal, especially in restrictive settings like the emergency room and inpatient settings.

Many new substances of abuse with unique effects are constantly emerging on the market. It is hence important for clinicians to keep themselves updated regarding the types and nature of substances of abuse that are available to their patients. These are widely available, often legally available, and have little peer-reviewed scientific research about them (136). Today's new substances of abuse include "research chemicals" such as synthetic amphetamines, cannabinoids, and cathinones. These chemicals can be purchased in pure form over the internet or in gas

stations and "head shops" in most states. Synthetic amphetamines are marketed as "plant food", synthetic cathinones as "bath salts", and synthetic cannabinoids as "incense". These products are usually sold in professional-looking packaging bearing labels such as "not for human consumption" (138), and are increasingly being abused by patients with schizophrenia (139). Synthetic cannabinoids, so-called "new marijuana" or 'Spice' (137), are becoming increasingly popular in Europe (140), Japan (141), and the United States (142). Spice products contain a plant substrate onto which is sprayed one or more synthetic cannabinoids, such as JWH-018 or CP47,497 (142). These chemicals have no safety data in human or animal species. Spice is becoming increasingly popular because it is legal to purchase online or in local head shops, is not detected in standard drug tests, and produces psychological effects similar to herbal cannabis. There have been no studies of Spice users or outcomes of use, but a number of case reports suggest using Spice can lead to feelings of anxiety, panic, hallucinations, and vomiting (143). One report describes a man with schizophrenia who had a psychotic episode purportedly triggered by smoking Spice (144). Spice contains synthetic cannabinoids that are much more potent than Δ9-THC and which unlike THC are full agonists at brain cannabinoid receptors. Furthermore, while herbal cannabis contains cannabidiol, a compound that may attenuate the psychotomimetic effects of THC (145), 'Spice' does not.

Specific to comorbid SUD and schizophrenia, Every-Palmer et al. (139) interviewed 13 patients with schizophrenia spectrum disorders (mean age 29) in a forensic rehabilitation facility about their use of Spice. All subjects had a history of cannabis use as well as use of Spice (139). The researchers showed that 69% of subjects experienced psychotic symptoms following use of Spice. Fifty-four percent considered Spice to be an "herbal or natural product" (Spice is in fact synthetic). There were few reports of anxiety (15%) or tolerance (23%), and no reports of withdrawal symptoms. The authors also mentioned that Spice is slightly more expensive than cannabis, and the psychoactive effects are shorter in duration (1-2 hours).

The future in treatment of schizophrenia and comorbid substance use disorders offers exciting new possibilities with the identification of new molecular targets. Antiaddiction vaccines show promise in being able to target drug dependence by preventing the drug from crossing the blood-brain barrier and thus, having negligible effects on brain physiology (146). Vaccines for cocaine and nicotine addiction are currently undergoing clinical trials, while vaccines for methamphetamine and heroin addiction are still in preclinical development.

Conclusions

The purpose if this review was to provide clinicians with up to date information on the epidemiology, consequences, reasons for, and treatment of comorbid SUDs in patients with schizophrenia.

- Patients with schizophrenia have high rates of SUDs.
- SUDs have a negative impact on the course and expression of schizophrenia.
- Patients with schizophrenia may be more vulnerable to SUDs because of reward dysfunction.
- The self-medication hypothesis, according to which schizophrenia patients use substances to "treat" core symptoms of the disorder, is not supported by current evidence.
- Given the high rates of SUDs in schizophrenia, the default should be to evaluate every patient for exposure to substances and to have a high degree of suspicion for substance misuse.
- The clinical assessment should be complemented with laboratory tests to probe substance use.
- Integrating substance abuse treatment with treatment for schizophrenia is recommended.
- The combination of pharmacotherapy and behavioral interventions is also preferred.
- The limitations of existing treatments combined with a paucity of knowledge about the vexing problem of comorbid SUDs and schizophrenia warrant further research on this topic.

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