Psychosis among substance users

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Purpose of review

This work reviews the evidence that substances of abuse can cause psychosis in nonpsychotic persons. The review is based on the concept that psychosis exists in continuum. Studies examining substance use in, or its effect on, already psychotic individuals were not reviewed.

Recent findings

A substantial proportion of substance users experience psychosis. Use of cocaine, amphetamines, cannabis and alcohol seems to be associated with greater risk for psychosis. Severity and duration of use, age at the time of first use and vulnerability to develop psychosis by virtue of familial, possibly genetic and personality factors seem to be the determinants for the development of psychosis. Epidemiological and preliminary biological studies suggest that cannabis is a component cause in the development of schizophrenia. Evidence for the causative role of other substances is less systematic.

Summary

There exists strong evidence that abuse of substances is associated with greater risk for psychosis and preliminary evidence for their causative role in the development of psychosis. More systematic examination of this issue is likely to throw light on the neurobiology of psychosis and possibly help the vulnerable population in primary prevention.

Keywords

psychosis, risk, substance abuse

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Abbreviations

DAT	dopamine transporter
MAP	methamphetamine
MDMA	3,4-methylenedioxymethamphetamine
NMDA	*N*-methyl-D-asparate
PCP	phencyclidine

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Introduction

Psychosis and substance abuse co-occur more frequently than can be explained by chance alone [1,2]. This may be because substance abusers are at a higher risk of developing psychosis and also because psychotic patients are at a high risk of developing the tendency for substance abuse. This review focuses on the former issue: psychosis among users of alcohol and illicit substances, namely, cannabis, amphetamines, cocaine, opioids, phencyclidine (PCP), hallucinogens and inhalants. Such differentiation of co-occurring problems is, no doubt, artificial as common vulnerabilities are likely to underlie the development of both disorders.

Knowledge about psychotic experience among substance abusers is important in several ways. Abused substances act on specific neurotransmitter systems. Studying the mechanism by which they impact these systems to produce psychosis could provide important clues about the pathophysiology of psychotic disorders. Information on the psychotogenic properties of specific substances may be useful in evaluating the risk of developing psychosis among drug users. Violence, aggression and crime are known to be more frequent among persons who have both psychotic symptoms and tendency for substance use than either alone [3,4]. Knowledge about the frequency of psychosis among users of different substances and their specific vulnerabilities may be useful from a forensic psychiatric perspective.

Although much research is taking place on psychosis in relation to certain substances like cannabis and amphetamines, there has been little recent research regarding other drugs. For each substance reviewed here, we begin with the review of important research and expert opinion, regardless of the year of publication; we follow that with an examination of the literature from the past few years. The concept that psychosis exists in a continuum rather than as an all-or-none phenomenon has gained popularity in the recent past [5]. In consonance with this approach, four different lines of research can be identified. They include the study of (a) psychotic experiences among healthy volunteers upon experimental exposure to substances, (b) transient psychotic experiences among epidemiological or clinical populations of substance abusers, (c) short-lasting syndromes of substance-induced psychoses and (d) the causative role of these substances in schizophrenia and related psychoses.

Alcohol

Alcohol is the most commonly abused psychoactive substance [6]. Persons abusing alcohol may experience psychotic symptoms in relation to several clinical conditions, each involving, possibly, different mechanisms: intoxication, withdrawal, delirium tremens, Wernicke–Korsakoff syndrome, alcohol-induced psychotic disorders and alcoholic dementia. Not surprisingly, alcohol dependence was predictive of psychotic experience in a general adult population survey in Great Britain [7]. The reported two-fold higher risk was independent of other risk factors for psychotic symptoms including drug dependence, suggesting that alcohol dependence *per se* doubles the risk of psychotic symptoms. In a clinic-based study of adults attending an urban general medical centre, Olfson *et al.* [8] found that patients with psychotic symptoms were significantly more likely to have alcohol-use disorders than patients without psychotic symptoms (12.9 versus 5.0%). They were also more likely to have other psychiatric disorders. The relative contribution of alcohol and psychiatric disorders toward the expression of psychotic symptoms is, however, unclear. Surprisingly, in this study drug-use disorder was not associated with greater risk of psychotic symptoms – perhaps due to the small number of drug abusing participants in the sample.

Although the occurrence of alcoholic hallucinosis has been noted for centuries, its nosological status is not yet clear [9]. Little research regarding this has been published in recent years. Tsuang *et al.* [10] reported a prevalence of 7.4% among patients in an alcohol treatment programme. Patients with alcoholic hallucinosis were younger at the onset of alcohol problems, consumed more alcohol per occasion, developed more alcohol-related life problems, had higher rates of drug experimentation and used more of other drugs than alcohol users without hallucinosis. The severity of dependence increased the risk for hallucinosis.

Soyka *et al.* [11–13] have consistently shown thalamic hypoperfusion on positron emission tomography (PET) scans in a small series of patients with alcoholic hallucinosis. The specificity of this finding to hallucinosis is questionable because thalamic abnormalities have been demonstrated in other disorders involving alcohol abuse as also with hallucinations not involving alcohol abuse [14,15]. Kathmann *et al.* [16] observed shorter P300 latencies in participants with a prior history of hallucinosis than normal participants and in persons with a prior history of delirium tremens. The authors hypothesized a state of brain hyperactivity in participants who are prone to hallucinosis. Unfortunately, this interesting result has remained unreplicated. In summary, a substantially greater proportion of alcohol abusers experience psychosis compared to nonabusers. The nosological status of alcoholic hallucinosis requires clarification, and more research on epidemiology and pathophysiology of this common clinical problem is needed.

Amphetamines and related stimulants

Amphetamines act on the brain predominantly by stimulating the release of dopamine. As perturbations of dopamine have been aetiologically linked to the development of psychosis, it follows that abuse of stimulants might be associated with a greater risk of developing psychotic symptoms. It has been known for decades that abuse of amphetamine is associated with the development of psychosis with schizophrenia-like symptoms [17]. A recent cross-national study, while confirming the observation of high prevalence of delusions (77.4%) and hallucinations (72.6%) among persons with methamphetamine (MAP) psychosis, also showed that a substantial proportion of them experience negative symptoms [18].

In a large study from a psychiatric hospital and a detention centre in Taiwan, Chen and colleagues [19] found that 40% of the MAP users in their sample met the criteria for amphetamine-induced psychosis. Most participants had used MAP at least 20 times in a year and none had psychotic symptoms before they started using MAP. The psychotic state lasted for less than a month following abstinence in over 80% of those afflicted. The risks for the development of amphetamine-induced psychosis were younger age at onset, larger dosage and premorbid schizoid/schizotypal traits. Abnormal premorbid traits predicted longer periods of psychosis postabstention. A related report from the same sample [20••] showed that family members of patients with methamphetamine-induced psychosis had a five times greater morbid risk for schizophrenia than users without psychosis. This followed a significant trend of incremental risk. Relatives of those who occasionally used MAP had the least risk. Relatives of regular users with short-lasting psychosis had an intermediate risk, whereas relatives of those who had prolonged psychosis had the greatest morbid risk for schizophrenia. MAP users' family loading for schizophrenia proportionately increased the likelihood of their developing psychosis and similarly influenced the length of psychosis postabstinence. It is possible that those with a high family loading for schizophrenia tend to start using MAP earlier in their lives and use it more heavily. This in turn might lead to the development of more severe and prolonged psychotic symptoms. This investigation therefore did not rule out the possibility that what is inherited could be the vulnerability to use MAP earlier and more heavily and not the vulnerability to develop psychosis *per se*.

How stimulants may cause psychosis is now being elucidated. MAP inhibits the dopamine transporter (DAT),

thus increasing dopamine levels in the synaptic cleft [21]. A PET study of patients with MAP psychosis, abstinent for 2 months, showed that the ratio of D2 receptor density of striatum to that in the frontal cortex was significantly less. This study [22] also suggested that MAP reduced D2 receptor density and the latter recovered with prolonged abstinence. Sekine *et al.* reported a significant reduction of DAT in the striatum and nucleus accumbens [23], orbitofrontal and dorsolateral prefrontal cortices [24] in abstinent MAP users. The magnitude of this reduction was associated with the severity of positive symptoms and also with the duration of MAP use. Similar findings on DAT reduction in basal ganglia have been reported by Volkow *et al.* [25]. These findings are in keeping with a hypothesis that longer exposure to MAP causes reduction of DAT, which in turn causes increased psychotic symptoms. Reduction in postsynaptic D2 receptor availability is also reported among MAP users [26]. To sum it up, recent research on MAP psychosis and the effects of MAP on the brain has provided important leads to the pathophysiology of psychosis.

Cannabis

The effects of cannabis, one of the most commonly used illicit drugs, have traditionally been seen as benign. Several recent reports have, however, attributed a more sinister role to cannabis use in the development of schizophrenia. Several prospective studies have reported greater prevalence of psychotic symptoms in cannabis users than in control groups. Two birth-cohort studies from New Zealand have shown consistent results in this respect. Arseneault *et al.* [27] reported that the risk of experiencing symptoms of schizophrenia at the age of 26 years is greater in those who were using cannabis at ages 15 and 18 years. Fergusson *et al.* [28••] reported that after adjusting for several risk factors for psychotic symptoms, those with a history of cannabis use in the past 12 months had an increased rate (1.6–1.8 times higher than nonusers) of psychotic symptoms at ages 18, 21 and 25 years. In a 3-year follow-up of a general population of the Netherlands, van Os *et al.* [29] studied 4045 psychosis-free persons. Baseline cannabis abuse predicted 'any psychotic symptom', 'severe psychotic symptom' and 'clinically significant psychotic symptom' (deemed to need treatment) during the follow-up period. This investigation also showed a strong dose–response relationship between cannabis use and psychotic symptoms. Finally, Ferdinand *et al.* [30••] conducted a 14-year follow-up study of 1580 children and adolescents randomly drawn from the Dutch general population. They found that cannabis use in individuals who did not have psychotic symptoms before they began using cannabis predicted future psychotic symptoms. Additionally, psychotic symptoms in those who had never used cannabis before the onset of psychotic symptoms also predicted future cannabis use.

Several reports focus on 'toxic' psychosis following heavy use of cannabis, which is characterized by disorientation, mild impairment of consciousness, dream-like euphoria, hallucinations and fragmented thought processes [31–33]. Similarly, there are many reports on acute psychosis resembling acute schizophrenia following cannabis use – cannabis was supposed to induce a short-lasting functional psychosis [34,35]. Patients with the latter condition differ from those with toxic psychotic in not having altered sensorium and disorientation. Both the disorders resolve by themselves upon abstinence. Although it is conceivable that cannabis was causative in toxic psychosis, there seems to be no compelling evidence to believe that it was causative in acute psychoses – such patients could well have developed the disorder even if they had not used cannabis.

In the past decade, there has been a deluge of reports from across the globe associating cannabis use with schizophrenia. The temporal precedence of cannabis use to the development of schizophrenia – a crucial issue in establishing causality – is clear in the prospective studies. The classical study of Andreasson *et al.* [36] was followed by longer term (27 years) follow-up of this cohort of Swedish conscripts [37]. In both studies, use of cannabis was associated with higher risk of development of schizophrenia. This association remained, even when the analysis was limited to those who developed schizophrenia 5 years after conscription (to rule out the possibility of conscripts using cannabis during the prodrome of schizophrenia). In a similar study on Israeli conscripts, Weiser *et al.* [38] found an association between adolescent use of cannabis and later development of schizophrenia. The Dunedin Birth-Cohort Study [27] showed an association between cannabis use at ages 15 and 18 years and development of schizophreniform disorder at age 26 years. Such an association was not found either for depression or for drugs other than cannabis. Two meta-analyses and systematic reviews [39•,40•] found a consistent, two-fold greater risk for psychosis among cannabis users.

Overall, there seems to be overwhelming evidence that cannabis use is associated with subsequent development of schizophrenia or psychotic symptoms. It is common belief that cannabis is neither necessary nor sufficient for the development of schizophrenia. Population-attributable fraction of schizophrenia for cannabis use is about 8%, meaning that we could reduce the incidence of schizophrenia by 8% if we were to completely eliminate cannabis use [39•]. None of the above evidence can, however, refute the hypothesis that there may be a single risk factor, which increases the chances of persons both using cannabis and later developing schizophrenia.

Certain individuals are particularly vulnerable to develop psychosis after cannabis use. Verdoux *et al.* [41] showed

that among students using cannabis, those who had higher vulnerability to develop psychosis had greater likelihood to experience unusual perceptions and feelings of influenced thought than those with lesser vulnerability. Caspi *et al.* [42••] showed that a functional polymorphism in the catechol-*O*-methyltransferase (*COMT*) gene is likely to moderate the influence of adolescent cannabis use on developing adult psychosis. Carriers of the COMT valine^{158} allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. In individuals homozygous for methionine allele, cannabis had little psychotogenic effect. Moreover, the gene × environment interaction was not found for use of cannabis.

Summing it up, there seems to be little doubt that at least a part of the long-known association between cannabis use and schizophrenia is because of the causative role that cannabis has on the development of schizophrenia.

Cocaine

Studies on cocaine abusers in clinical settings report that more than half of such individuals experience paranoia and hallucinations [43–45]. Even in community samples, the rates of psychotic experience are comparable [46•]. Among patients who attend psychiatric emergency services, nonschizophrenic cocaine abusers are reported to have as severe hallucinations as schizophrenic patients who do not abuse cocaine [47]. Believing that their drug-using behaviour is being watched and they are being followed, hallucinations, in keeping with these delusions, are typical of cocaine-induced psychosis. This is so typical that it may be used as an important tool to differentiate it from schizophrenia. Presence or absence of Schneiderian first-rank symptoms can be another differentiating point between the two [48].

Those who develop psychosis with cocaine are likely to be men, have a greater duration and amount of use [49], have greater psychosis proneness [50] and have a lower body mass index [51]. Intravenous abusers have more paranoia and hallucinations than nonintravenous abusers [46•,49]. This may, however, just be a reflection of greater levels of cocaine use rather than the effect of the route of administration [46•]. Cocaine-induced psychosis shows sensitization – psychosis becomes more severe and occurs more rapidly with continued cocaine use [43,45]. Interestingly, sensitization occurs only with psychosis and not with other effects of cocaine [44]. Cocaine abusers who experience sensitization to psychotogenic properties of cocaine seem to have less naturally occurring craving and are likely to reduce their cocaine and other substance use [52•]. Unlike with cannabis and amphetamines, reports of cocaine being aetiologically linked to chronic psychosis are very rare [53,54].

Other drugs

Research reports regarding psychoses among users of other drugs including opioids, psychedelics like PCP, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA) among others, and inhalants are sparse. This may be either because their use is less common (e.g. LSD, PCP) or because psychosis is uncommon (e.g. MDMA, benzodiazepines). Nevertheless, we attempt to review the recent literature on this. Although there are some case reports of psychoses following administration of opioid analgesics for different medical conditions (e.g. [55–57]), psychoses among opioid abusers seem to be rare. Hardly any report on 'opioid-induced psychoses' is found. In a study, in which 716 treatment-seeking opioid abusers were assessed using structured diagnostic interviews, the rate of schizophrenia was in fact 0.3% [58], much less than that found even in general population. This was similar to the rates reported about a decade back [59,60]. More recently, Sorensen *et al.* [61] found a rate of 8.5% for psychosis during a follow-up spanning over two decades in a cohort of those who were treated for opioid addiction. The results of this study are, however, difficult to interpret as it is not clear whether, in many of these, psychoses preceded the onset of opioid addiction.

3,4-Methylenedioxymethamphetamine

The use of this psychedelic is becoming increasingly popular because it is perceived to be a 'safe' drug. Several reports of MDMA-associated psychoses (e.g. [62]) have, however, raised alarm. More research on this has obvious public health importance.

Phencyclidine and ketamine

Certain *N*-Methyl-D-asparate (NMDA) glutamate receptor agonists like phencyclidine have long been known to produce psychotic states with features of schizophrenia including delusions, hallucinations, thought disorder and negative symptoms [63,64]. This observation contributed to the NMDA hypothesis of schizophrenia [65]. Recent experimental studies [66–68] using subanaesthetic doses of ketamine resulted in dose-dependent production of neuropsychological defects, positive symptoms and thought disorder. In another study, Krystal *et al.* [69••] investigated the interactive effects of ketamine with amphetamine on healthy volunteers. As expected, ketamine produced positive and negative symptoms, thought disorder and impairment in executive functions, and amphetamine produced positive symptoms, thought disorder and psychomotor activation. When given consecutively, the drugs had an additive effect on the production of thought disorder, less than additive effect on psychotic symptoms and no interaction in causation of negative symptoms. Amphetamine reduced the cognitive impairment produced by ketamine. These results suggest that

different dimensions of schizophrenia have distinct neurobiological substrates.

Inhalants

Many case reports suggest that inhalation of toluene containing volatile solvents is associated with development of psychoses similar to schizophrenia, which may be irreversible in many cases [70,71]. Systematic research is needed to examine if psychosis can be attributed to toluene after factoring out other risk factors.

In a recent investigation of the relative psychotogenic properties of commonly abused substances (Thirthalli *et al*., unpublished data) involving out-of-treatment drug abusers in St Louis, USA, intravenous drug users, crack-cocaine users and heroin snorters were contacted by outreach health workers and assessed using Composite International Diagnostic Interview – Substance Abuse Module (CIDI-SAM) [72]. The majority of the participants had a history of multiple-substance dependence. They were assessed for psychotic symptoms lasting for at least 1 month or occurring on several occasions while using or withdrawing from specific substances. When the participants were dependent on more than one substance, psychotic symptoms specifically in relation to each of them were assessed. The prevalence of psychotic symptoms in the context of specific substances was 85% for hallucinogens, 82% for PCP, 80% for cocaine, 64% for cannabis, 56% for amphetamine, 54% for opioids, 41% for alcohol and 32% for sedatives. Prevalence of psychotic symptoms increased with the increasing severity of dependence, reaching up to 100% among those severely dependent on cocaine. Participants dependent both on cocaine and another drug were likely to report experiencing psychotic symptoms more from cocaine than from the other drug, except for PCP and hallucinogens. This study provides preliminary evidence regarding the relative psychotogenic properties of different abused substances.

Conclusion

Our review suggests that psychosis in the aftermath of substance abuse is fairly common. Some substances are more likely to be associated with greater risk of psychosis, namely, cocaine, amphetamines, cannabis and alcohol. Despite different study designs and tools of assessments, the prevalence rates seem to be fairly comparable across studies. The most systematic evidence is available for the causative role of cannabis in psychosis – at the very least, cannabis appears to be a component cause of schizophrenia. The propensity to develop psychosis appears to be a function of the severity of use and of dependence. Family loading for psychosis and personality diatheses have important contributions. This area is significant with possibilities to explore the biology of psychosis. Unfortunately, the research into neurobiological and genetic underpinnings of substance-related psychoses has been sparse and has not yet generated a coherent theory of psychosis.

References and recommended reading

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 325).

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This study examins two competing hypotheses of schizophrenia, namely, NMDA hypothesis and dopamine hypothesis. The results and discussion are interesting; they show that symptom dimensions of schizophrenia are likely to have distinct neurobiological substrates.

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