Psychostimulant-Induced Chronic Schizophrenia-Like Disorder

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Abstract

The acute psychotogenic effects of psychostimulants are well documented. However, the chronic psychotogenic effects of psychostimulants are less well understood. In this review we examine the available literature in search of evidence for and against the proposition that chronic use of stimulants could lead to a chronic psychotic disorder clinically resembling schizophrenia. Based on the review, we conclude that the evidence for an amphetamine-induced chronic psychotic disorder is strong. The exact relationships between genetic predisposition, other environmental factors, continued drug use, and the maintenance of the syndrome have not been established. The evidence for a cocaine-induced chronic psychotic disorder is far less compelling as compared to amphetamine abuse.

Key Words: Psychosis, Schizophrenia, Substance Abuse

Introduction

Psychostimulant models of psychosis are important animal models for human schizophrenia (1-4). Angrist and Gershon (5) observed that the symptomatology of experimentally-induced amphetamine psychosis closely resembles endogenous schizophrenia. Similarly, Snyder (6) considered amphetamine psychosis to be a "model" schizophrenia due to the strong similarity of its clinical features to paranoid schizophrenia.

Whether or not psychostimulant use can cause a chronic psychotic disorder in humans that is clinically similar to schizophrenia remains an open and important question *with diagnostic, therapeutic, and prognostic implications*. In this review, we attempt to determine if there is enough evidence in the literature to support the notion that abuse of psychostimulants can cause chronic psychotic disorders. We also examine whether drug-induced psychotic states can be self-sustaining (i.e. autonomous) or require continued drug use. If continued drug use is necessary, what level of use is needed in order to sustain the syndrome?

Our systematic review of the literature focused on human and animal studies that investigated the relationship between psychostimulants and the development of psychotic symptoms. Literature reviews and experimental studies were included; however, case reports and editorials were not. We performed electronic searches from the earliest available dates through January 2007 utilizing PubMed, Medline, and Ovid. Search terms included: AMPHETAMINE, COCAINE, METHAMPHETAMINE, STIMULANT, PSYCHOSIS, DRUG-INDUCED PSYCHOSIS, and SCHIZOPHRENIA.

It is well accepted that acute intoxication with psychostimulants (i.e. methamphetamine [MA], amphetamine, or cocaine) can result in acute emergence of psychotic symptoms (7). While this can lead to diagnostic confusion in the emergency room, careful history taking and urine and blood tests are usually sufficient to alert the clinician to the possibility of a drug-related problem (8). While these authors presented evidence that some clinical differences can be discerned between cocaine users with psychotic symptoms and schizophrenia patients with and without cocaine intoxication, the evidence of reliability of such diagnostic differences remains lacking. Depending solely on the clinical presentation is not advisable at this stage of knowledge. A period of follow-up in the absence of continued drug use is also usually sufficient to confirm the diagnosis (9). Of course, the prevailing assumption is that drug-induced syndromes will clear with continued abstinence while an idiopathic syndrome, although showing some improvement with abstinence, is unlikely to clear altogether. This assumption will be examined below. We will discuss the issue of acute intoxication in as much as it may provide clues to the nature of the psychopathology to be seen in more protracted cases of drug-induced psychosis.

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The difficulties of researching the longer-term effects of stimulants were highlighted in two Japanese studies (10,11). The widespread use of high-dose injected MA led to hospital admissions of individuals with chronic psychosis that persisted after substance use had ceased. The authors noted that many of these individuals qualified for a diagnosis of schizophrenia. However, genetic risks and other possible contributing factors and the presence or absence of pre-drug use evidence of increased risk (e.g. presence of prodromal symptoms or schizotypal traits) were not assessed. It should be noted that large series of chronic cocaine-dependent individuals with emergent psychotic disorders cannot be found in the literature.

In a recent study, Barnes and colleagues (12) examined the history of drug or alcohol use in 152 patients diagnosed with either schizophrenia or schizophreniform disorders. They reported that 90% of the patients with a history of any type of substance abuse reported the use of cannabis. This study highlights the inherent difficulty in assessing causality in a population largely characterized by polydrug use, increased life stressors, and possibly other factors like head injury. Polydrug use may indeed be a fundamentally different problem than use or addiction of a single substance. Indeed, in another study, psychosis proneness differed between cocaine-dependent and cocaine- and alcohol-dependent individuals (13). The cocaine-alcohol group was significantly more likely to experience a paranoid psychosis with cocaine use. While not systematically examined in clinical populations, animal experimentation suggests that even short duration of abuse of PCP-like agents may greatly potentiate the behavioral effects of psychostimulants (14).

Epidemiology

Nakatani and Hara (15) observed that the large-scale MA abuse that has occurred in Japan provides an excellent opportunity to further our understanding of these disorders. MA abuse became widespread shortly after World War II, but almost disappeared during the mid-1950s due to strict legal enforcement. However, beginning in the early 1970s, a new MA epidemic developed. Nakatani and Hara noted that some interesting differences regarding patients' profiles have been found between the first and second epidemics. Many reports during the postwar period have focused on the clinical resemblance to schizophrenia and manic-depressive illness. However, another study (16) concluded that typical exogenous symptoms such as clouding of consciousness, amnestic syndrome, impaired intellectual functioning, and physical signs are generally not apparent in patients with MA intoxication.

Barr and colleagues (17) noted that one of the most prominent effects of MA abuse on cognitive function pertains to the development of drug-related psychosis. Aside from the sudden psychosis-inducing effects of high doses of MA, an enduring form of psychosis can also develop. These authors noted that studies from Japan found that between 36% and 64% of MA users who have experienced psychotic symptoms continue to present with these symptoms for more than ten days after the cessation of MA use, even though the MA is eliminated from the blood stream in less than five days (18). Another study involving female inmates in Japan found that 21% of those with MA psychosis remained in a psychotic state for more than six months. Another 49% returned to their premorbid state, but experienced "flashbacks" (i.e. spontaneous recurrence of psychotic symptoms that would fit criteria for a paranoid-schizophrenia psychotic relapse) during their 15–20 months of incarceration (18). Barr and colleagues note that studies in Japan show that MA users with MA psychosis are much more likely to experience psychotic symptoms again if they use MA and are also more likely to have a psychotic relapse when confronted with stressful situations, even years after cessation of MA use (17). Furthermore, MA users with persistent or recurrent psychotic symptoms become vulnerable to environmental stress and may benefit from antipsychotic medication in a manner similar to individuals with schizophrenia (18).

Yui and colleagues (2) suggested that further evidence for stimulant-induced psychosis could be found in the MA abuse epidemic in Japan shortly after World War II, when huge military stores of MA found their way to the open market in Japan, leading to widespread abuse. A significant number of MA abusers developed psychosis that did not resolve with discontinuation of drug use, and many patients required years for recovery. Sato (19) reported that 10% of chronic heavy amphetamine users developed a chronic psychotic disorder lasting more than six months after cessation of amphetamine use.

A recent study examined the relationship between psychosis and drug-dependence in a large sample of prison population in England. Farrell and colleagues (20) surveyed the clinical condition and history of drug use of 503 individuals. They found that first use of amphetamines or cocaine before the age of 16 years, and severe cannabis or cocaine-dependence to be related to an increased risk of psychosis. These data agree with our recent finding regarding the significance of the age of first use as a risk factor for developing acute psychotic symptoms with cocaine use (21). In contrast, severe dependence on heroin was associated with a reduced risk for developing a psychotic syndrome (20).

Schuckit's (22) comprehensive review of comorbidity between substance-use disorders and psychiatric conditions found psychotic symptoms to occur in about 40% of amphetamine-dependent patients, especially with higher doses. Schuckit noted that stimulant-induced psychoses are very likely to clear within several days to about a month of abstinence. Only 1%–15% of patients with stimulant-induced psychoses maintain some psychotic symptoms after a month. Schuckit speculated that this could reflect the fact that approximately 1% of people in any group will develop schizophrenia, or could be the consequence of the precipita-

tion of longer-term psychotic disorders in predisposed individuals. However, 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.

Clinical Descriptions of Amphetamine- and Cocaine-Induced Psychoses

Early Observations of Amphetamine Psychosis

In 1958, Connell (23) published his seminal monograph on amphetamine psychosis. He reviewed thirty-six clinical case reports of patients developing psychosis following amphetamine use. Of these thirty-six patients, nine developed a protracted psychotic syndrome persisting more than two months after withdrawal from amphetamine, and in three subjects this prolongation of psychotic symptoms was "indefinite." In an attempt to compare clinical pictures of amphetamine-induced psychosis and schizophrenia, Bell (24) studied fourteen patients with amphetamine-induced psychosis. These patients did not have any psychotic symptoms prior to abusing drugs. Three of these patients continued to show psychotic symptoms for many months after they ceased to take amphetamine.

Ellinwood Jr. (25) interviewed twenty-five subjects with chronic amphetamine-dependence. Of the twenty-five, eight were classifiable as no-psychosis and ten as amphetamine-induced psychosis. Ellinwood Jr. described hyperamnesis (i.e. acute and focused memory of the psychotic experience). Clearly, not all amphetamine users developed psychosis (although all of them were suspicious at some time), and there was no continuum of severity toward psychosis. Fear and terror were major symptoms mentioned by psychotics. Philosophical concerns increased as patients became progressively psychotic. Both auditory and visual hallucinations were noted. Gross distortion of bodily image was highly correlated with psychosis. Finally, changes in libido varied greatly, but an increase in libido and polymorphous sexual activity most often preceded psychosis. Charles-Nicolas (26) studied the histories and clinical pictures of twenty-five amphetamine-abusing chronic psychotic patients. He found seven of them to have had no psychotic tendencies before the addiction. These patients were followed in his center for several years prior to the onset of psychosis.

Observations of Amphetamine Psychosis in Japan

Methamphetamine psychosis (MAP) involves paranoid-hallucinatory states indistinguishable from paranoid schizophrenia, with residual volitional disturbances (e.g. loss of spontaneity and idleness). Paranoid-hallucinatory states persist after the pharmacological effects of MA have worn off and readily reappear upon re-injection of MA. Individuals with a history of MAP were also observed to experience spontaneous recurrence of their paranoid-hallucinatory states in response to stress (27).

MAP patients may develop acute paranoid psychotic exacerbation after long-term abstinence with minimal use (at times a single dose) of amphetamine or alcohol (10). One of the patients in this cohort relapsed without evidence for amphetamine use (10). Persistent personality changes may develop in patients with chronic amphetamine use and paranoid-hallucinatory state. These observations provide strong presumptive evidence that certain effects of chronic stimulant abuse can persist long after cessation of use (28). Tomiyama (29) found postamphetamine chronic psychotic patients to have fewer negative symptoms as measured by the Scale for the Assessment of Negative Symptoms. Tomiyama suggested that these patients not be labeled as schizophrenic, recommending instead the term "residual psychosis."

The findings of Tomiyama (29) are in contrast with Srisurapanont and colleagues (30) who showed that a substantial proportion of such patients do experience negative symptoms. This group found premorbid schizoid/schizotypal traits to be a serious risk factor for developing a protracted post-abstinence psychotic syndrome. The same group provided additional evidence implicating a premorbid vulnerability to psychosis, as well as to early and heavy amphetamine use in individuals developing chronic or prolonged post-abstinence psychotic syndromes (31). Indeed, these researchers showed that family members of patients with MAP had a five times greater morbid risk for schizophrenia than users without psychosis.

Harris and Batki (7) showed that in a sample of 19 subjects who met *DSM-IV* criteria for amphetamine- or cocaine-induced psychosis, all had persecutory delusions with 95% having bizarreness to the delusions, 53% had grandiose, and 32% had somatic delusions. Of the entire sample, 95% experienced auditory hallucinations, with 32% describing voices running commentary, and 58% hearing more than one voice conversing with each other. Additionally, 68% had visual, 26% experienced tactile, and 26% olfactory hallucinations. While negative symptoms were less than what would be expected in a group of schizophrenia patients, they were detectable (particularly anergia) and correlated significantly with length of stay in the emergency room or subsequent hospitalization.

Yui and colleagues (27) observed that paranoid-hallucinatory states gradually disappear, although idleness and emotional flattening tend to increase one month after the cessation of MA use (32). Goto (33) described twenty-three patients with persisting MAP who suffered from residual symptoms such as emotional blunting or manic-depressive states following a drug-free period of 4.6–9.7

years. Utena and colleagues (34) reported that 5% of patients with MAP were hospitalized for years after the cessation of MA use because of their volitional disturbances (e.g. loss of spontaneity and idleness). Although at odds with Connell's (23) original observations that amphetamine psychosis is never prolonged after excretion of MA in the urine (suggesting that continued use of MA is essential to maintain the psychosis syndrome), some have suggested that the development of MAP may be etiologically related to persisting brain damage or changes in brain metabolism induced by MA (28). Yui and colleagues conclude that the Japanese experience of MAP, in which psychotic symptoms can develop with the progress of MA-induced brain damage in the course of chronic MA use, therefore differs from Connell's experience. However, the authors note that, in Japan, MA is injected without any other substance, with most users re-injecting before the effects of the previous MA injection have diminished. These authors conclude that such exclusive and repetitive use of MA may engender enduring vulnerability to paranoid-hallucinatory states, leading to spontaneous recurrences of MAP.

Disturbance of consciousness due to MA abuse was reported in two patients by Nakatani and Hara (15). These authors noted that, in both cases, mental status changed, passing through three distinct stages: restlessness and insomnia, hallucinatory paranoid state, and disturbance of consciousness following a period of amphetamine use. In addition to delirium during intoxication, Askevold (35) described abstinence delirium in amphetamine abusers, reporting a latency period between the beginning of abstinence and the onset of delirium of between three and ten days followed by a period of delirium of between four and eighteen days. Fatal delirium has also been reported in association with cocaine intoxication (36).

Recent Studies of Amphetamine Psychosis

In a recent systematic review, Curran and colleagues (37) concluded that there is clear evidence that, "irrespective of the individual's mental state, a large enough dose of a stimulant drug can produce a brief psychotic reaction, usually lasting only hours and being self-limiting in the majority of individuals."

The pattern of stimulant abuse most commonly associated with the induction of psychosis is the initial use of lower doses, typically administered in an escalating manner and ultimately leading to multiple binges or runs (38, 39). Emergence of psychotic syndromes usually occurs during a binge. Chronic psychosis, on the other hand, may emerge during a period of abstinence. Flaum and Schultz (40) presented a demonstrative case in detail exemplifying a common clinical scenario that presents the clinician with a diagnostic dilemma. In summary, a teenage male with no evidence of increased risk for schizophrenia (i.e. no abnormal behavior including good school performance and good social skills and lack of family history of psychiatric disorders except drug use) began abusing amphetamine and marijuana on regular bases with occasional use of hallucinogens and cocaine for a period of about ten years. Family pressure was applied, and he stopped drug use. In a few weeks he began to develop paranoid ideations that became delusions. Delusions were non-bizarre at the beginning and progressively became more bizarre and hallucinations eventually also occurred. There was no evidence of continued amphetamine use, but marijuana was used occasionally. The patient also exhibited negative symptoms (withdrawal and alogia). The patient's positive symptoms responded well to haloperidol, but without effect on negative symptoms. Flaum and Schultz proposed that this case suggested an etiologic role for amphetamine and polysubstance use in the development of a chronic schizophrenia-like psychotic disorder. Whether some form of genetic liability to developing a psychotic disorder existed in this case could not be positively ruled out, and brings to focus the chicken-and-egg nature of the question raised here. Early work by Angrist and Gershon (5) suggested that a predilection to the psychogenic effects of stimulants is an important factor contributing to the emergence of these symptoms with stimulants use.

Clinical descriptions provided by Snyder (6) were similar to what has been provided in the literature except that stereotyped compulsive behavior was emphasized with patients often pacing back and forth with their mouths moving from side to side. The stereotyped compulsions seemed to be consistent in MAP (25). The presence of tactile hallucinations was also said to differentiate MAP from schizophrenia where such hallucinations are rare.

Cocaine-Induced Psychosis

Post (41) reviewed the evidence for cocaine-induced psychosis and its predeterminants. He reported that with chronic cocaine use, a syndrome of insomnia, painful delusions, and apathy can develop. This phase occurs during the transition from initial euphoria to paranoid psychosis. When the cocaine-induced paranoid psychosis is fully developed, it is almost indistinguishable from paranoid schizophrenia. Post stated that with cessation of cocaine use, hallucinations usually stop, but delusions may persist. Satel and Edell (42) showed that heavy cocaine users who experience transient paranoia while intoxicated may be at higher risk for development of psychosis than cocaine users who do not experience paranoia. On the other hand, the development of a cocaine-induced chronic psychosis seems to be rare (43). Rounsaville and colleagues (44) found that only four of 298 chronic cocaine users had received the diagnosis of schizophrenia or schizoaffective disorders. All four patients were males.

Long-Term Follow-Up Studies

Long-term follow-up studies are sparse in this literature. In a six-year follow-up study, McLellan and colleagues (45) reported that chronic use of stimulants led to the development of a psychotic disorder that was not secondary to acute intoxication. They had control groups composed of patients who used depressants or narcotics. Although a significant number of patients who used sedatives developed serious depression, none of the patients in either control group developed a psychotic disorder similar to that seen in stimulant users. Typical of cocaine abusers, their delusions and hallucinations tend to be related to their drug use behavior (e.g. they are being watched). Absence of first-rank Schneiderian symptoms (e.g. thought withdrawal and thought broadcast) have been noted in cocaine-intoxicated patients who are experiencing psychotic symptoms (46). Retrospectively, formal thought disorder and bizarre delusions significantly predicted a diagnosis of schizophrenia, with odds ratios (OR) of 3.55:1 and 6.09:1, respectively. Suicidal ideation (OR = 0.32:1), intravenous cocaine abuse (0.18:1), and a history of drug detoxification (0.26:1) or methadone maintenance (0.18:1) demonstrate inverse relationships with a schizophrenia diagnosis (47). As there are no reports of long-term follow up of large cohorts of patients with cocaine-induced psychosis, it is not known whether these differences from idiopathic schizophrenia would persist. Of interest is the observation that while cocaine-induced psychosis shows sensitization (i.e. psychosis becomes more severe and occurs earlier with repeated cocaine use), sensitization occurs only with psychosis and not with other effects of cocaine (48). Moreover, cocaine abusers who exhibit sensitization to the psychogenic effects of cocaine seem to have less naturally occurring craving and are likely to reduce their cocaine and other substance use (49). Unnithan and Cutting (50) found cocaine-induced psychosis and schizophrenia to be so distinct as to refute the concept of cocaine psychosis as a model for schizophrenia. They particularly highlighted the increased intensity of colors, change of light intensity, objects appeared more vivid, and macropsia and micropsia were reported by the cocaine-intoxicated individuals. They also stated that even if paranoia is present, it tends to be rather transitory.

Most recently, Schuckit (22) utilized a systematic review of manuscripts published in the English language since approximately 1970 in order to investigate the comorbidity between substance-use disorders and psychiatric conditions. Results of this review generally supported 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.

Imaging and Electrophysiology Studies

Given the dearth of well-defined cohorts of stimulant-induced psychosis patients, it is not surprising that neuropsychology, electrophysiology or imaging studies specifically addressing this population are few.

Neuropsychology

Yui and colleagues (27) found patients with a history of MAP showed impairment of selective attention, although with less cognitive deficit than schizophrenic patients. Similarly, in mild to moderate drug use in humans, no differences were found between the two drugs on cognition (51).

Electrophysiology

Iwanami and colleagues (52) found methamphetamine dependence correlated with P3a reduction (detection of novelty). Methamphetamine psychosis (MAP) was associated with reduced mismatch negativity (MMN/an indicator of pre-attentive ability to detect change in ongoing sensory input) and not P300. Earlier, the same group reported MAP subjects to have reduced P300 anteriorly while schizophrenia patients more posteriorly, suggesting differences in the orientation of the cerebral sources of the activity (53).

Iwanami and colleagues (54) investigated the auditory event-related potentials (ERPs) during a dichotic syllable discrimination task in sixteen unmedicated subjects in residual states following the remission of MA-induced paranoid-hallucinatory states. Extrapolation from these findings suggests some similarity in susceptibility to paranoid-hallucinatory states between MAP and schizophrenia. Similarly, abnormal ERPs, indicative of abnormal information processing, have been reported in abstinent cocaine-dependent individuals. Most notably, there is a deficit in inhibiting irrelevant incoming sensory input (sensory gating) (55). The finding was later replicated in a more racially mixed group (56). More recently, our group provided further evidence of a deleterious effect of chronic cocaine on gating of the P50 evoked response (57).

Electrophysiological studies in cocaine-dependent individuals suggest a complex mechanism for the development of psychosis in these subjects. Inhibition of incoming irrelevant sensory input (i.e. sensory gating) has been repeatedly demonstrated in schizophrenia patients (58). As mentioned earlier, a similar decrease in inhibitory capacity was demonstrated in abstinent cocaine users (55, 57). This decreased inhibition was correlated with psychosis proneness in this population (57). On the other hand, the initial studies utilizing transcranial magnetic stimulation (TMS) to examine cortical excitability in this group provided evidence of increased cortical inhibition (59). This finding was replicated in a larger sample and was interpreted as a compensatory protective mechanism against the epileptogenic properties of cocaine (60).

The findings of increased inhibition demonstrated via TMS and decreased inhibition demonstrated via evoked responses presented a dilemma for interpretation. A most recent study utilizing additional TMS-based measures of

cortical excitability, namely the paired-stimulus facilitation and inhibition, provided evidence consistent with increased excitability (or decreased inhibition) (61). Given that the paired-stimulus TMS technique has been rather strongly linked with cortical inhibitory-excitatory mechanisms, and that it is likely that sensory gating may be strongly influenced by subcortical mechanisms, we postulated that some form of a cortical subcortical imbalance in the excitatory-inhibitory balance may be important for the development of psychotic symptoms in cocaine users.

Imaging Studies

One CT study found no differences between drug-induced and idiopathic schizophrenia (62). Iyo and colleagues (63) examined the binding availability of 11C-N-methylspiperone using positron emission tomography (PET) in order to assess the role of dopamine D2 receptors in the striatum and serotonin S2 receptors in the frontal cortex, in susceptibility to MAP. These researchers suggested that an imbalance in the activity of the two receptors is related to susceptibility to MAP, and that a decrease of dopamine transporter in striatum may be related to MAP (64). Down regulation of D3 dopamine receptor function in critical brain areas has also been implicated in the process of sensitization (65).

Evidence for sensitization in humans is found in a small number of studies (66, 67). Strakowski and colleagues (66) showed that when two doses of a stimulant were given to volunteers free from psychosis, the second dose produced a greater psychotic response as measured by the BPRS—a "sensitized" response. Stimulant users studied by Brady and colleagues (68) reported psychotic symptoms occurring with lower doses over time. Yui and colleagues (27) concluded that the development of MAP may therefore be related to persisting brain damage or changes in brain metabolism induced by repeated MA use, and that studies of the clinical course and neurological basis of MAP psychosis may provide insights into the pathophysiology of schizophrenia.

Laruelle (69) described the role of endogenous sensitization in the pathophysiology of schizophrenia in his review of recent brain imaging studies. He observed that sensitization of mesolimbic dopamine systems has been postulated by several authors to underlie the development of dopaminergic abnormalities associated with schizophrenia. Laruelle noted that results of recent brain imaging studies indicate that schizophrenia is associated with increased amphetamine-induced dopamine release, and that this exaggerated response was detected in patients experiencing an episode of clinical deterioration, but not in clinically stable patients (69). Laruelle asserted that because increased stimulant-induced dopamine release is a hallmark of sensitization, these results support the view that schizophrenia is associated with a process of endogenous sensitization. He further postulated that amphetamine-induced hyperactivity of the dopaminergic system sustained over a certain period of time is in itself sufficient to induce a psychotic state in otherwise healthy humans, although the role of an underlying vulnerability to this effect cannot be entirely ruled out.

Treatment

Barr and colleagues (17) described the scarcity of data regarding treatment for MAP, noting the absence of controlled trials. These authors noted that the standard of care in this area parallels the management of acute psychosis from other etiologies, such as schizophrenia. The current trend is for initial treatment with antipsychotics, with a bias toward the atypical antipsychotics as first-line treatment. To date, there has been no evidence that typical antipsychotics have efficacy in decreasing craving among substance-abusing psychotic patients. Evidence for atypical antipsychotic use suggests some measure of efficacy, but remains limited to case reports and small open-label patient series. The length of appropriate pharmacological intervention is largely unstudied, and no consistent guidelines exist in the literature. Barr and colleagues reported a small case series indicated that antipsychotic treatment beyond the acute psychotic episode may protect against future psychotic episodes, even at very low doses.

Beresford and colleagues (70) treated ten patients with comorbid schizophrenia and drug use with aripiprazole for eight weeks in an open-label design. They showed that in those who completed the trial (60%), positive urine tests dropped significantly after two weeks. Both mean cocaine- and alcohol-craving scores also dropped significantly, with a positive correlation between dropping psychosis and dropping craving scores. Green and colleagues (71) examined the acute response to haloperidol and olanzapine in ninety-seven first episode psychosis patients with comorbid substance abuse. They found no difference between typical and atypical medications, but an overall less likelihood of responding when compared to patients without drug use comorbidity. These findings are in contrast to a report by Brown and colleagues (72) where twenty-four dually-diagnosed patients who were on typical antipsychotics were randomized to either continue or discontinue the typical agent. Quetiapine was substituted when necessary in those who discontinued the typical antipsychotic. They report that those discontinuing a typical antipsychotic had significant reduction in drug craving as compared to the other patients. Brown and colleagues further reported that typical antipsychotic discontinuation combined with a quetiapine switch was associated with reduced drug craving. Finally, animal work suggests a possible role for serotonin in treating this condition. When cocaine and risperidone were coadministered to rats, the effects of cocaine seemed to have been blocked (73).

Barr and colleagues (17) proposed that current research indicates that people presenting with co-occurring disorders,

Table 1 Summary of Literature Findings Regarding Psychostimulant-Induced Chronic Schizophrenic-Like Disorder

• Acute intoxication with psychostimulants can result in acute emergence of psychotic symptoms.
• Careful history taking and urine and blood tests are usually sufficient to identify the possibility of a drug-related problem and help avoid diagnostic confusion.
• Depending solely on the clinical presentation is not advisable when presented with the possibility of substance-induced psychotic symptoms.
• A period of follow-up in the absence of continued drug use is usually sufficient to confirm the diagnosis.
• First use of amphetamines or cocaine before the age of 16 years, and severe cannabis or cocaine-dependence, may be related to an increased risk of psychosis. In contrast, severe dependence on heroin was associated with a reduced risk for developing a psychotic syndrome.
• Stimulant-induced psychoses are very likely to clear within several days to about a month of abstinence. Only 1%–15% of patients with stimulant-induced psychoses maintain some psychotic symptoms after a month.
• Research from Japan has shown that family members of patients with methamphetamine psychosis had a five times greater morbid risk for schizophrenia than users without psychosis.
• The pattern of stimulant abuse most commonly associated with the induction of psychosis is the initial use of lower doses, typically administered in an escalating manner and ultimately leading to multiple binges or runs.
• The current trend for psychostimulant-induced psychotic symptoms is for initial treatment with antipsychotics, with a bias toward the atypical antipsychotics as first-line treatment.
• Early treatment and retention of stimulant users in mental health care services is recommended to prevent the development of a chronic psychotic condition.

such as MAP, warrant specific treatments that deal with both the psychosis and addiction issues. In fact, the best outcomes stem from programs that are considered evidence-based and that integrate mental health and substance-abuse treatment. Barr and colleagues noted that most MA treatments investigated so far have used only an "addiction" treatment model for stimulant dependence and have excluded people with comorbid mental health problems, such as persistent or recurrent psychotic symptoms. Further research is required to develop a more thorough understanding of the profiles of people who suffer from persistent or recurrent MAP.

If sensitization is indeed the underlying mechanism for psychostimulant-induced chronic schizophrenia-like disorder, then early treatment and retention of stimulant users in mental health care services would appear to be desirable to prevent the development of a chronic psychotic condition. There is indeed a lack of good quality evidence as to whether this approach can be effective. A Cochrane review found no relevant trials (74). A potentially important finding in rats (without parallel human studies as yet) is the demonstration that low-dose clozapine or haloperidol can block the induction of behavioral sensitization to amphetamine in rats (75). This finding has potential implication for future preventive use of such drugs in individuals with evidence of increased susceptibility to developing a psychotic disorder.

Conclusions

We conclude that the literature does suggest that abuse of psychostimulants can result in, or increase the susceptibility for, a state of chronic psychosis. It is also likely that the abuse of psychostimulants in combination with other drugs may further enhance the chances for developing such syndromes. We further conclude that substantial evidence exists that abuse of amphetamines, as the sole drug of abuse, can result in a chronic psychotic disorder. On the other hand, the evidence for a cocaine-induced chronic psychosis is less compelling. The exact relationship between premorbid vulnerability and the persistence of symptoms in the absence of continued drug use or the degree of use needed to sustain a psychotic syndrome are also not well characterized yet.

That psychosis exists in a continuum rather than an "all or none" phenomenon is a plausible idea (76). Based on a stress-diathesis model, we propose that the eventual development of a chronic psychotic disorder in an individual with a history of drug use is likely to be multifactorial with the specific substances used, the pattern of use (including duration and age of onset of regular use, dose, and pattern of episodes of use), and environmental stress interact with the individual's own degree of psychosis proneness to generate different degrees of severity of psychotic processes. It is quite possible that the combination of drugs used, possibly with the exceptions of MA and hallucinogens that seem to be capable of producing chronic psychotic syndromes on their own, is a crucial factor in the nature of the emergent pathology.

Seeman and colleagues (77) identified factors other than genes and psychostimulants that are associated with psychosis or schizophrenia, including prenatal influenza,

prenatal drug treatment (e.g. reserpine), and obstetrical complications.

The fact that some evidence of abnormality may be evident up to ten years prior to onset of frank symptoms makes this task extremely challenging (78). While disentanglement of the chicken-and-egg problem of chronic stimulant-induced psychosis is indeed very difficult, work by Hafner and colleagues (79) showed that a rather accurate determination of the onset of behavioral change can be determined. This allows the close examination of the chronological associations of drug use and the development of psychotic or even prodromal schizophrenia symptoms.

In conclusion, much research is necessary in order to tackle the many remaining unanswered questions. The most obvious need is for the development of cohorts of well-characterized patients that can be followed longitudinally from the time of first contact. While obviously not an easy task, it is necessary to establish the natural course of these syndromes particularly in the absence of continued drug use. Many crucial factors must be characterized in these individuals: estimate of genetic risk (i.e. family history), other risk factors (e.g. head injury, child abuse, ADD/ADHD). Once well-defined cohorts are established, other neuro-investigative (neuropsychology, electrophysiology or imaging), as well as treatment studies can be more easily performed.

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