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Treatment of psychosis induced by a potent hallucinogen- N,N-dimethyltryptamine (DMT)

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Introduction

Current use of 'designer' drugs: hallucinogens, stimulants, cannabinoids

Media reports over recent years have frequently focused on new trends in illicit drug use, typically with a sensationalist flavor. Thus, news media have breathlessly announced the latest drug craze to sweep the nation: 'bath salts', 'meow-meow', 'spice', and others. [1,2] These compounds are typically psychostimulants, hallucinogens, or synthetic cannabinoids (for review, see Rosenbaum).[3] Interestingly, the emergence of many of these compounds is a result of drug prohibition combined with significant numbers of people who are seeking to use illicit drugs: the novel drugs are designed to pharmacologically mimic established drugs of abuse while retaining sufficient chemical distinctiveness to skirt existing legal prohibition.In addition to a market-driven mechanism to satisfy existing demand, a substantial and perhaps growing number of drug users are interested in exploring the subjective effects of compounds with hallucinogenic properties. Websites such as www.erowid.org provide online forums for recreational users to

share experiences, thereby encouraging further drug use among the discussants. The hallucinogen class includes novel compounds such as methoxetamine, methoxydine and 4-OH-MET,[4,5] in addition to older compounds such as lysergic acid diethylamide (LSD), psilocybin and ketamine.[6] An interesting member of the hallucinogen class is N,N-dimethyltryptamine ('DMT'). Recent data indicate that DMT use is significant, at least among drug-using populations, with approximately 9% lifetime use in a large sample of anonymous online reports in 2012, compared to 26% for ketamine and approximately 40% for lysergic acid diethylamide (LSD) and psilocybin.

DMT: the "spirit molecule"

DMT is an indolealkylamine that is found in several plant species,[7] in addition to the central nervous systems of several mammal species including humans.[8] Despite a well-documented ethnographic history of use and chemical identification and synthesis in Europe approximately 60 years ago (for review, see Szára),[9] DMT failed to reach widespread levels of use in earlier decades. More recently, however, the profile of DMT has risen considerably likely due to a combination of ethnography, scientific research and mainstream popularization. Specifically, the 2010 documentary "DMT: the spirit molecule", the efforts of syncretic Brazilian religions to gain legal approval for use of ayahuasca in their religious ceremonies in the United States,[10] and the internet forums mentioned above.

- **Traditional use of DMT**

DMT has been used for centuries by native peoples of the Americas, for example as the active ingredient of ayahuasca (oral route) or cohoba (nasal route),[11] for spiritual and healing purposes.[12,13] Beginning in 1956, DMT was first studied extensively by Szára, working in Hungary at that time. DMT has been used recreationally – generally smoked – in Western countries from the mid-1960's onward,[14] and this remains the most common route of administration. Anecdotal reports from well-known users of hallucinogens[15,16] provided vivid accounts of brief, truly hallucinatory experiences, often consisting of perception of travel to distant universes or planets and interactions with non-human entities. These anecdotal reports are consistent with subjective experiences under controlled conditions which have been described as dissociation from the physical body in combination with a complete replacement of "ongoing mental experience" in such a way as to be "more convincing than…reality or dreams."[17]

- **Pharmacology of DMT**

DMT activates multiple 5-hydroxytryptamine (5HT) receptor subtypes including 2A, 2C and 1A [18,19,20] and also exhibits biologically relevant binding affinities for multiple other 5HT receptor subtypes such as 1A, 1B, 1D, 6 and 7 (for review see Halberstadt and Geyer).[21] Convergent in vitro and in vivo pharmacologic data from animals and humans support the hypothesis that the hallucinogenic properties of DMT are mediated via 5HT2A and, to a lesser

extent, 5HT1A receptor activation. Although no pharmacokinetic data could be located for smoked DMT, a study of oral administration of freeze-dried ayahuasca reported that the time to maximum plasma concentration coincided with the peak subjective effects. The psychoactive experience of smoked DMT is reported as having a very rapid onset with peak effects around 1 minute; the experience is over by approximately 20 minutes after smoking DMT,versus peak effects at 2-5 minutes and total duration of 20-60 minutes after intramuscular or intravenous administration.

Hallucinogen use disorder: addiction and addiction-related disorders

The word "addiction", although still used both in the literature and in common parlance, has been replaced in many journals, articles and importantly the DSM, with substance use, substance dependence, or substance disorder. Indeed, it was during the revision of the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition that the word 'dependence' was selected over "addiction"– reportedly by a single vote.[22] More recently, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)[23] has simplified the relevant terminology by collapsing substance use and substance dependence together in favor of substance use disorder that is graded in severity. The criteria that are used to define a substance use disorder in DSM-5 can be assigned to groups that reflect loss of control, social impairment, risky use and pharmacology (i.e., tolerance and withdrawal). By contrast, the DSM-5 criteria for hallucinogen use disorder do not contain the withdrawal criterion, because there is no empirical data to support withdrawal phenomena even after frequent use of hallucinogens. In addition to use disorders, both hallucinogens and psychostimulants can induce psychosis and probably all drugs of abuse can induce mood disorders. Thus, in addition to substance use disorder per se, additional disorders induced by use of the substance can be critical complicating factors when considering treatment goals and strategies.

A review of the currently available literature identified a single case of first-onset psychosis in a man with a positive family history of psychotic illness, and a year-long history of increasing frequency of use of tobacco, cannabis, methamphetamine and a self-prepared plant material that probably contained DMT.[24] Unfortunately, this case does not provide details of treatment strategy or goals. Given the increasing levels of use of DMT and other hallucinogens, the frequency of DMT- and other hallucinogen-induced psychopathology is likely to rise in the future. The case reported below outlines one such presentation, and in contrast to the report identified above, provides greater details of presenting symptoms and successful treatment, and far greater confidence that the most accurate diagnosis is substance-induced psychosis.

Summary

The above discussion makes clear that, with the exception of the withdrawal criterion, hallucinogen use disorder is defined using the same criteria for other substance use disorders – in other words, addiction – in DSM-V. Further, for most drugs of abuse and perhaps even more so for hallucinogens, substance-induced disorders such as psychotic or mood disorders become an additional target of therapy that may be key to reaching all of the other treatment goals. The following example illustrates the psychotogenic effects of repeated use of the hallucinogen DMT and, importantly, provides an effective treatment strategy comprising not only acute pharmacologic treatment of the presenting psychosis, but also a prolonged rehabilitative phase to address chronic patterns of illicit drug use and provide education and vocational training to increase the chances of successful maintenance of sobriety and a return to optimal functionality.

Case presentation: DMT-induced psychosis

Past psychiatric and social history

Mr. K was a middle-aged Caucasian male with no psychiatric history other than a recent 72-hour hold that was placed when the patient had been smoking DMT and was found acting in a bizarre fashion. Since then, the patient had continued to smoke DMT, and was brought to the emergency room by police, on a 72-hour hold, again after acting bizarrely in public. Although Mr. K had not been diagnosed with any major psychiatric illness in the past, he had received treatment for substance use disorders – alcohol, vicodin, cocaine, ecstasy - several years previously, and had been convicted of driving while intoxicated. Since that time, the patient had smoked marijuana and more recently began using DMT. In addition, there was a positive family history for bipolar disorder and obsessive compulsive disorder, in addition to alcoholism. Socially, Mr. K had grown up in a violent neighborhood, and had engaged in physical violence both as a child (multiple school suspensions) and as an adult (several convictions for assault and domestic violence). Failing to graduate high school, he served in the armed forces for several years, receiving an honorable discharge. Since that time, Mr. K had transitioned through a number of jobs, none lasting more than a few years. Similarly, Mr. K's longest romantic relationship had lasted for no more than two years. At the time of hospitalization, Mr. K was unemployed, had been evicted from his apartment, and had recently suffered the loss of a parent. During this period, he continued to smoke marijuana and, over the three weeks prior to admission, DMT.

Presenting Symptoms

The patient was brought into the emergency room for psychiatric evaluation, by local police. On initial interview, the patient appeared agitated and underweight, and behaved bizarrely (crawling on the floor examining scraps of paper, repeatedly touching a specific piece of furniture, and occasionally singing). He denied abnormal perceptions, suicidality or homicidality but exhibited a marked disorientation to time. Thought content was significant for references to navigation by the stars and increased religious content; thought processes were loose, disorganized and frequently tangential. Shortly thereafter, he became agitated and after receiving emergent

medication was admitted to inpatient psychiatry for further evaluation. In follow-up interviews over the next 12 days, the patient endorsed paranoid and grandiose delusions, claimed to be able to read minds and believed he could orchestrate distant events and persons by adopting specific body postures. During this time, the patient was hyperverbal and intrusive. In later interviews, the patient reported that DMT use was "real interesting…like traveling to another dimension" and also referred to interacting with "aliens". Of note, laboratory studies at admission revealed an elevated creatinine kinase (2732 units/L), which resolved over the next five days, most likely attributable to the posturing behavior that the patient was engaging in prior to, and for several days after, admission. Finally, urine toxicology was positive for benzodiazepines, likely due to emergent medication after presentation as urine was obtained on the 3rd hospital day, but otherwise negative. It is important to note that DMT is not detected in routine urine toxicology.

Acute Treatment Phase

The patient was started on quetiapine to address his psychotic symptoms, rapidly uptitrating from 100 mg at bedtime to 400 mg at bedtime and ultimately to 100 mg in the morning and at noon, and 600 mg at bedtime from the 10th hospital day onward. It should be noted that over the first 10 days, the patient also received intramuscular olanzapine (10 mg) four times and risperdal (rapidly dissolving formulation, 2 mg po) twice. In addition, gabapentin 300 mg po tid was initiated to target the patient's reported anxiety from Day 4 onward. Divalproex sodium was started at 500 mg at bedtime to suppress ongoing and historical impulsivity, as evidenced by his history of violent behavior and substance abuse. Finally, hydroxyzine was available at 50 mg po qhs for sleep, with good effect. By hospital day 14, the patient began to deny his previous delusional beliefs, and gained some insight and judgement into his illness, as evidenced by attributing said delusions to his recent drug use. Patient also began planning for the future. With no further psychotic symptoms, and exhibiting normal behavior and functioning on the unit, the patient was discharged to a residential drug treatment program, with follow-up outpatient psychiatric care, after 21 days in hospital.

Long-term Treatment Phase

The patient was discharged to a residential program that provides an array of services, focused on establishing and maintaining long-term sobriety and ultimately achieving a healthy, functioning and drug-free life. For example, in addition to individual and group counseling, residents are taught communication, anger management and other skills. Also, residents are provided vocational assessment and training, in addition to legal and social (e.g., housing placement) services. Six months after discharge, and still engaged in the residential program, the patient remains symptom- and drug-free, and has begun to taper his quetiapine treatment under the supervision of his outpatient psychiatrist.

Discussion

'Designer' drug use and addiction

As discussed above, the increasingly widespread use of novel hallucinogens and psychostimulants is likely to provide new challenges to psychiatrists and other healthcare providers. Further, illicit use of these compounds meets all of the criteria of substance use disorders except withdrawal, even if use of hallucinogens is often not as frequent and compulsive as use of established drugs of abuse and psychostimulants. Finally, the often severe and functionally impairing effects of hallucinogen use on psychosis, perceptual disturbance and mood disorders, require an acute treatment phase focused on alleviation of these substance-induced disorders prior to a longer-term focus on drug use per se (even though this phase is likely to include a significant continuation of the acute treatment phase strategy). The case outlined here provides a highly useful and illustrative example of this two-pronged approach to treatment.

Treatment of DMT-induced psychosis

The psychotic symptoms and agitated behavior reported and observed at presentation, and for approximately 10 days after admission and initiation of antipsychotic treatment, in a middle-aged man with no history of a psychotic disorder (substance-induced or otherwise) were most likely attributable to use of DMT, a hallucinogen that exhibits significant agonist properties at 5HT2A and 5HT1A receptor subtypes, among others. The patient's subjective reports of his experiences are consistent with those reported during acute DMT intoxication. Interestingly, although prolonged posturing of the patient may explain the rhabdomyolysis, the chemically and pharmacologically related hallucinogen LSD is thought to cause rhabdomyolysis.[25] With likely increasing use of DMT in the United States, the incidence of DMT-induced psychosis will likely also increase. The present case provides at least one example of the effectiveness of a commonly-used second-generation antipsychotic in ameliorating acute psychotic symptoms and, at six months post-discharge, maintenance of a symptom-free state in the context of ongoing participation in a residential drug-treatment facility.

Precipitant: DMT vs. marijuana

In the present case, the patient was smoking DMT in combination with marijuana. Marijuana-induced psychosis is recognized in DSM-5, where it is characterized as typically involving persecutory delusions, elevated anxiety, emotional lability and depersonalization, and short-lived: lasting several days at the most. As detailed above, the reported symptoms appear distinct from the typical features of cannabis-induced psychosis as described in DSM-5. Nonetheless, it was suggested in a recent critical review of the literature that "cannabis psychosis" may lack qualitative differences from other psychotic disorders.[26] In the present case, urine toxicology was negative for cannabinoids, ruling out recent use. In addition, although there was a time lag of three days from admission until urine toxicology was performed, the absence of cannabinoids in the urine suggests that the patient was likely using far less marijuana than he reported or had stopped a considerable time before presentation, given the prolonged presence of cannabinoids in

urine after use.[27] Unfortunately, DMT cannot be detected on routine urine toxicology. Thus, although the concomitant use of marijuana should be considered a caveat, the biochemical data support the attribution of the described psychosis to DMT use.

Diagnostic considerations

Finally, the facts of the present case clearly lead to a diagnosis of substance-induced psychotic disorder per DSM-5, rather than another psychotic disorder. Specific criteria are met as follows: (A) the presence of delusions and hallucinations (only one of these is required); (B) the emergence of the symptoms during or soon after DMT intoxication and the ability of DMT use to induce such symptoms; (C) the timeline of symptom onset (during or soon after intoxication) and resolution (approximately two weeks) combined with the lack of personal history; (D) the absence of delirium; (E) clinically significant distress and functional impairment.

Conclusion

The present case report illustrates an important example of substance-induced psychosis in a 42-year-old Caucasian man with no past psychiatric history that is most likely attributable to the use of N,N-dimethyltryptamine (DMT), a potent hallucinogen that is being used increasingly commonly. As such, emergency room, primary care and psychiatric inpatient and outpatient services are likely to see a significant increase in similar cases. As the current example makes clear, the substance-induced psychosis resolved during treatment with the antipsychotic quetiapine, consistent with a previous case report of substance-induced psychosis,[28] allowing the crucial long-term process of rehabilitation. At this time, the patient remains symptom- and drug-free six months after discharge as he continues a residential rehabilitation program.

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EDITOR'S NOTE: Dr. Paterson won the 2014 Shirley Hatos 21st Century Psychiatry Prize for the above article.