N,N-Dimethyltryptamine–Induced Psychosis

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Background: N,N-dimethyltryptamine (DMT) is a 5-hydroxytryptamine 2A and 1A receptor agonist that exhibits potent psychoactive properties in humans. Recreational use of this drug has increased precipitously and is likely to result in an increase in patients presenting with substance-induced psychoses. The present case provides an early example of substance-induced psychosis attributable to repeated use of DMT.

Case: A 42-year-old white man, with no significant past psychiatric history, was brought to the emergency department by the police and was found to exhibit disinhibited behavior, elevated affect, disorganized thought process, and delusions of reference. Laboratory studies revealed elevated creatinine kinase level indicative of rhabdomyolysis. The patient endorsed recent and repeated use of DMT, as well as long-term *Cannabis* (marijuana) use. Over the course of the next 3 weeks, the patient was successfully treated with quetiapine for psychosis, divalproex sodium (Depakote) for impulsivity, gabapentin for anxiety, and hydroxyzine for sleep, which resulted in the resolution of his symptoms and development of reasonable insight and judgment. Approximately 6 months after discharge, the patient remained treatment compliant, as well as drug and symptom free.

Conclusions: This case report illustrates an important example of substance-induced psychosis that resolved with antipsychotic treatment in a 42-year-old white man with no past psychiatric history likely attributable to the use of DMT. Given the increasing use of this substance, the emergency department, primary care, and inpatient services are likely to see a significant increase in similar cases.

Key Words: DMT, *Cannabis*, hallucinogen, substance-induced psychosis, quetiapine

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BACKGROUND

The hallucinogen N,N-dimethyltryptamine (DMT) is an indolealkylamine that is found in several plant species,[1] as well as the central nervous systems of several mammal species including humans.[2] Despite a well-documented ethnographic history of its use[1] and chemical identification and synthesis in Europe approximately 60 years ago (for review see Szára[3]), DMT has failed to reach widespread levels of use in past decades. Recent data, however, 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,[4] compared with 26% for ketamine and approximately 40% for lysergic acid diethylamide and psilocybin. Currently, most DMT is obtained in crystal form and smoked alone or with tobacco or *Cannabis* (marijuana). Prices are approximately $15 to $30 for a single hit (estimated 15–60 mg, smoked).[5] The reasons underlying possible increases in DMT use are unclear, although it may be part of the burgeoning popularity of "designer drugs"—hallucinogens and stimulants (generally) that are legal for a brief period solely by virtue of their innovative nature and are largely undetected on standard toxicology screens. N,N-dimethyltryptamine is a schedule 1 substance in the United States. It is a well-known hallucinogen likely because of a combination of ethnography, scientific research, and mainstream popularization from the 2010 documentary "DMT: the spirit molecule"; the efforts of syncretic Brazilian religions to gain legal approval for the use of ayahuasca in their ceremonies in the United States[6]; and internet forums where recreational users share their experiences such as www.erowid.org.

Anecdotal reports from well-known users of hallucinogens (eg, McKenna and McKenna[7] and Shulgin and Shulgin[8]) provided vivid accounts of brief hallucinatory experiences characterized by perception of travel to distant universes or planets and interactions with nonhuman entities. These anecdotal reports are consistent with subjective experiences under controlled conditions, which have been described as a dissociation from the physical body with a complete replacement of "ongoing mental experience" in such a way as to be "more convincing than… reality or dreams."[9] The psychoactive experience of smoked DMT is reportedly rapid and short-lived, with peak effects around 1 minute and complete resolution by approximately 20 minutes after inhalation.[8,10] Slightly delayed effects are reported after intramuscular and intravenous administration.[3,6] 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.[11]

In the present case, a male patient with no history of a psychotic disorder, substance induced or otherwise, presented in the emergency department with psychotic symptoms and an elevated creatinine kinase level after recent and repeated use of DMT.

CASE

Mr K. was a 42-year-old white male with no psychiatric history other than multiple substance use disorders until he was placed on an involuntary legal hold for bizarre and disorganized behavior after smoking DMT that ultimately led to his hospitalization.

Mr K. had a positive family history for alcoholism, bipolar disorder, and obsessive-compulsive disorder. He grew up in a violent neighborhood and engaged in physical acts of violence both as a child and as an adult. Failing to graduate high school, he served in the armed forces for several years, received an honorable discharge, and thereafter transitioned through a number of short-lived jobs and a series of unstable romantic relationships. Beginning around the age of 19 years, Mr K. began using alcohol (later convicted for driving while intoxicated) and tobacco, adding *Cannabis* around age 22 years (later fined for possession of *Cannabis*), and at age 27, he began using 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). He briefly misused hydrocodone (Vicodin tablets, also containing acetaminophen). Upon successful completion of a residential treatment program at age 39 years, Mr K. gained employment and began attending regular alcoholics anonymous meetings. Nonetheless, he resumed smoking *Cannabis*, and 3 weeks before hospitalization, he began using DMT. He estimated that he had smoked DMT a maximum of 10 times, reporting that he had impulsively purchased the DMT in the street

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near his home. At the time of hospitalization, Mr K. had a number of psychosocial stressors including recent unemployment, eviction from his apartment, and the death of his mother.

The patient was brought by local police to the emergency department for psychiatric evaluation. On initial interview, the patient appeared agitated and underweight; he behaved bizarrely and exhibited a marked disorientation to time. Thought content was significant for delusional references to being "navigated by the stars" and increased religious content; thought processes were loose, disorganized, and frequently tangential. He denied abnormal perceptions, suicidality, or homicidality. Shortly afterward, he became extremely agitated warranting emergency medication and was admitted to inpatient psychiatry for further evaluation. In follow-up interviews over the next 12 days, the patient endorsed paranoid and grandiose delusions; he 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 his DMT use was "real interesting… like traveling to another dimension" and also referred to interacting with "aliens." Laboratory studies upon admission were notable for an elevated creatinine kinase level (2732 units/L) that resolved over the next 5 days, which was most likely attributable to the posturing behavior that the patient was engaging in before, and for several days after, admission. Finally, the urine toxicology result was positive only for benzodiazepines, likely because of the use of emergency medication upon presentation as his urine was obtained on the third hospital day. The atypical delay in obtaining urine was secondary to the patient's agitated behavior in the emergency department. N,N-dimethyltryptamine would not have been detected at any time point on a standard screen. The detection window for amphetamine and cocaine can extend to 3 days, and therefore a negative screen at day 3 is most likely confirmatory of patient's denial of cocaine or amphetamine use before admission; phencyclidine use is categorically ruled out, with a detection window of up to 14 days.

The patient was started on quetiapine to address his psychotic symptoms, rapidly up-titrating from 100 to 400 mg at bedtime and ultimately to a regimen consisting of 100 mg in the morning and at noon, and 600 mg at bedtime from the 10th hospital day onward. During the first 10 days, the patient also received intramuscular olanzapine 10 mg on 4 occasions and risperidone orally disintegrating tablets 2 mg twice for severe and moderate agitation, respectively. These additional antipsychotics were used as standard local practice for pharmacological treatment of severe and moderate agitation and do not reflect treatment-refractory symptoms. Furthermore, 6 instances of emergency medication in 10 days do not make the patient exceptional and do not suggest a treatment-refractory illness. In addition, oral gabapentin 300 mg three times a day was initiated to target the patient's reported anxiety from hospital day 4 onward.[12] Divalproex sodium (Depakote) was started at 500 mg at bedtime to suppress impulsivity symptoms.[13] Finally, hydroxyzine was available at 50 mg at bedtime for sleep,[14] with good effect. Of note, both gabapentin and hydroxyzine were used for anxiety and sleep, rather than benzodiazepines, because of the patient's significant substance use disorder history. By hospital day 14, the patient began to deny his previous delusional beliefs and demonstrated improved insight, understanding that his delusions were caused by his recent drug use, and improved judgment as evidenced by medication compliance and future planning for ongoing treatment. The patient was discharged on hospital day 21 because he exhibited cooperative behavior, appropriate functioning on the unit, and no further psychotic symptoms present. The patient was discharged to a residential drug treatment program with scheduled follow-up outpatient psychiatric care. Six months after discharge, the patient remained symptom and drug free and had begun to taper his quetiapine treatment.

DISCUSSION

The psychotic symptoms and agitated behavior that were present 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 the 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.[7–9] Interestingly, although the patient's rhabdomyolysis was thought to be secondary to his prolonged posturing, the chemically and pharmacologically related hallucinogen lysergic acid diethylamide has also been known to cause rhabdomyolysis.[15] With an increase in the use of DMT in the United States, the incidence of DMT-induced psychosis is highly likely to increase also. The present case provides at least 1 example of the effectiveness of a second-generation antipsychotic in ameliorating acute psychotic symptoms and the maintenance of a symptom-free state at 6 months after discharge. It should be noted that in addition to quetiapine, the patient received limited (4 and 2, respectively) doses of the antipsychotics olanzapine and risperidone. The patient was also chronically treated with an anticonvulsant for impulsivity and another for anxiety and an antihistamine medication for sleep.

In the present case, the patient was smoking DMT in combination with *Cannabis*. *Cannabis*-induced psychosis is recognized in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*),[16] where it is characterized as typically involving persecutory delusions, elevated anxiety, emotional lability, and depersonalization and as short lived—lasting several days at the most. As detailed previously, the reported symptoms seem distinct from the typical features of *Cannabis*-induced psychosis as described in *DSM-5*. It was suggested in a recent critical review of the literature that "*Cannabis* psychosis" may lack qualitative differences from other psychotic disorders.[17] In the present case, urine toxicology was negative for cannabinoids, ruling out recent use. In addition, although there was a time lag of 3 days from admission until urine toxicology was performed, the absence of cannabinoids in the urine suggests that the patient was likely using far less *Cannabis* than he reported or had stopped a considerable time before presentation, given that cannabinoids persist in the urine for prolonged durations after use.[18] Coupled with the prolonged course of the described psychosis, it seems unlikely that concomitant use of *Cannabis* contributed significantly to the substance-induced psychosis reported here.

Finally, the facts of the present case clearly lead to a diagnosis of substance-induced psychotic disorder per *DSM-5*[16] 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 2 weeks) combined with the lack of personal history; (*d*) the absence of delirium; and, finally, (*e*) clinically significant distress and functional impairment.

In conclusion, the present case report illustrates an important example of substance-induced psychosis in a 42-year-old white man with no past psychiatric history that is most likely attributable to the use of DMT, a potent hallucinogen that is being used more

commonly. As such, emergency, primary care, and inpatient services are likely to see a significant increase in similar cases. Emergency department physicians should have a high suspicion for drug-induced psychosis in persons who present as acutely psychotic, particularly when there is no psychiatric history and despite negative urinary toxicology (standard screens). As the current example establishes, the substance-induced psychosis resolved during treatment with the antipsychotic quetiapine, along with medications for impulsivity, anxiety, and sleep as indicated previously, and the patient remained symptom and drug free 6 months after discharge.

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