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Persistent Tinnitus after Inhaled N,N-dimethyltryptamine (DMT)

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ABSTRACT

This case report describes a 39-year-old male with remote history of polysubstance use disorder and depression who developed tinnitus after use of inhaled N,N-dimethyltryptamine (DMT). Although development of ear ringing was attributed to use on a single occasion, tinnitus occurred within the context of a larger self-experiment involving weekly microdoses of lysergic acid diethylamide (LSD). Distress and anxiety over the ear ringing prompted evaluation by an audiologist, primary care physician, and consultant psychopharmacologist. Tinnitus persisted for several months, although intensity and ability to cope with symptoms improved over time. A microdose of psilocybin mushrooms exacerbated tinnitus on two separate occasions, after which psychedelics were discontinued. Psychedelics are associated with a range of acute sensory changes including auditory phenomenon, although have not previously been associated with tinnitus in medical literature. Here, we present a probable case of tinnitus associated with DMT use and review potential underlying mechanisms connecting psychedelics and tinnitus.

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Introduction

Interest in researching the therapeutic use of classic psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and N,N-dimethyltryptamine (DMT) has increased in recent decades with several small clinical studies producing promising results for a variety of mental illnesses (Carhart-Harris and Goodwin 2017; Fuentes et al. 2020; Liechti 2017; Malcolm and Lee 2017; Thomas, Malcolm, and Lastra 2017). In recent clinical trials of psychedelic assisted psychotherapy, there have been no serious adverse events observed and adverse effects have been primarily transient and limited to the experience itself or the week after the experience (Mithoefer et al. 2019; Thomas, Malcolm, and Lastra 2017).

Use in unsupervised environments with psychedelics is still relatively safe and the majority of users do not suffer persistent adverse effects (Halpern, Lerner, and Passie 2018; Krebs and Johansen 2013a, Krebs and Johansen 2013b). However, for a variety of reasons including dose, dosing pattern, preexisting illness, set and setting, as well as amount of support available, persistent psychological phenomena have been reported including depression, anxiety, cognitive dysfunction, psychosis, mania, and hallucinogen persisting perceptual disorder (HPPD) (Dos Santos, Bouso, and Hallak 2017; Halpern, Lerner, and Passie 2018; Parrott 2012).

In parallel to positive research in moderate doses of psychedelics used in combination with psychotherapy, use of subperceptual doses of psychedelics or "microdosing" on a semi-chronic basis for performance enhancement, alleviation of depression, anxiety, as well as a host of other mental and even physical ailments has increased (Cameron, Nazarian, and Olson 2020; Fadiman and Korb 2019; Hutten et al. 2019). Use of psychedelics in microdoses is perhaps appealing to those less familiar with psychedelic substances to avoid navigating the intensity of full subjective experiences.

In one short-term study of persons that microdosed, self-reported symptoms of depression or anxiety were lower after 6 weeks, particularly on days of microdosing, yet they scored higher in "neurotic tendencies" than baseline (Polito, Stevenson, and Arnone 2019). Another study reported improved mood and focus as benefits along with physiological discomfort, increased anxiety, impaired mood, focus, or energy (Anderson et al. 2019). Other nonpsychedelic serotonin agonists such as fenfluramine and lorcaserin have been associated with chronic toxicities such as valvulopathy and cancer (Food and Drug Administration (FDA) 2020; Hutcheson et al. 2011; Kuypers et al. 2019; Nichols 2016). Therefore, microdosing is an experimental movement that may have unknown or unforseen long-term consequences. Here, we present a case study of persistent tinnitus associated with use of inhaled DMT within

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the context of a larger microdosing self-experiment as well as review potential mechanisms and corroborating internet anecdotes regarding psychedelics and tinnitus.

Case description

A 39-year-old Caucasian male presented to a psychopharmacology consultant due to a complaint of ringing in the ears or tinnitus. He reported use of inhaled DMT 16 days prior to presentation and described new onset of ringing in the ears beginning the day after DMT use. He stated intensity of ringing increased in the ears over the course of the day until it was "unbearable" by evening time, including a constant high-pitched ringing bilaterally as well as a chime sound in the left ear. He reported using DMT within the context of a larger self-experiment microdosing LSD. A timeline of psychedelic ingestion, doses, and frequency of use is detailed in Figure 1.

The patient reported difficulty hearing initially, having to stand near those talking to him to understand them. He endorsed brief "flashes" visually for 48 hours after the experience that were not bothersome. The patient denied feeling dizziness accompanied with the ringing. The ringing was initially painful, although he described it as "psychosomatic" due to his focus on the sound. The ringing was exacerbated by the presence of electronic devices. Although the patient was highly distressed by the ringing, he reported a paradoxical feeling of inner peace for approximately 7 days following the DMT experience.

He stated that 4 days prior to presentation he had visited an audiologist who conducted an audiogram, which ruled out hearing loss and resulted in diagnosis of tinnitus. He then visited his primary care physician (PCP) who concurred with the diagnosis, however, did not perform additional neurological testing. He was referred to psychological counseling for emotional support of his distress, although a plan was developed to follow up in a few months.

The patient underwent an in-depth follow-up interview 116 days after onset of tinnitus. His medical history included hypertension, which is associated with tinnitus, although he reported it was well controlled without use of antihypertensive medication (Figueiredo, Azevedo, and Penido 2016). He denied history of seizures or epilepsy, migraines, and tinnitus prior to DMT use. His psychiatric history included verbal and emotional abuse as well as neglect during childhood. At age 14 he was diagnosed with depression, anxiety, and suffered from a polysubstance use disorder. He used cannabis, methamphetamine, and alcohol chronically from age 14–20. During this time period he also reported sparing and intermittent use of cocaine and LSD, although he denied any noticeable persistent effects from the use of LSD (or any other substances) during this time. Between the ages of 20 and 24, the patient successfully addressed polysubstance use disorder in rehabilitation programs and was treated with psychotropic medications for depression and anxiety.

This remote history was followed by a 14-year period of sobriety in which he did not use drugs, alcohol, or psychotropic substances. He reported still having symptoms of depression and anxiety during this time period, although coped by using meditation and continued support from his addiction recovery community. Approximately 7 months prior to the incident DMT experience, he began LSD microdosing. He also used DMT several times at lower doses on other occasions

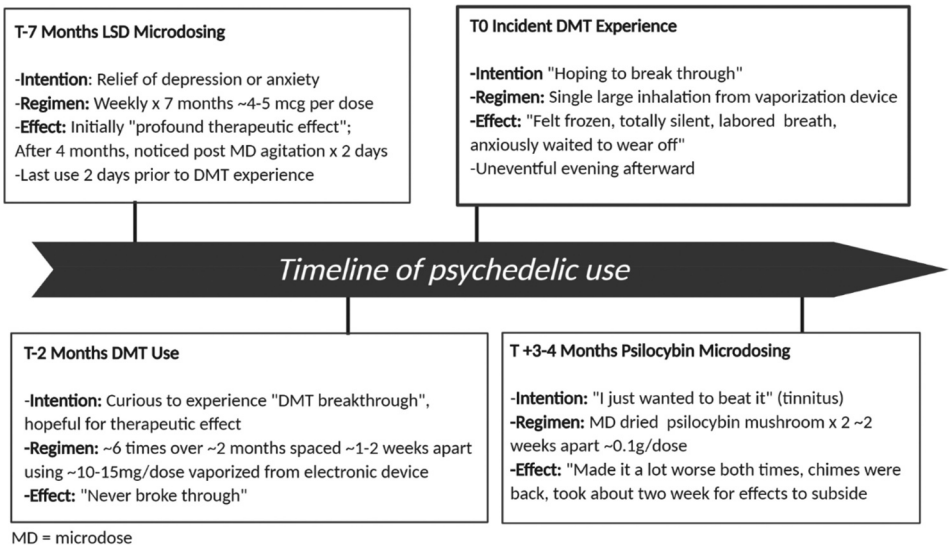

Figure 1. Timeline of Patient's Psychedelic Use.

prior to the experience associated with tinnitus. After he developed tinnitus he abstained from DMT use and trialed microdosing psilocybin, which reportedly exacerbated or worsened the tinnitus. All use of psychedelics was self-use in an unsupervised setting of the patient's private residence.

The patient was asked to recall how he had felt immediately after the tinnitus onset while filling out the Tinnitus Function Index (TFI), a validated scale to assess the severity and impact of tinnitus (Meikle et al. 2012). The patient's overall TFI score was 83.6 out of 100 (higher scores equate with more severe symptoms), with subscales (out of 100) of emotional distress, intrusiveness attributed to the tinnitus, and feeling a reduced sense of control scoring 100, 93, and 93, respectively. Thereafter the patient was asked to reflect on his current state, 116 days after the tinnitus onset. The emotional distress, intrusiveness, and a reduced sense of control decreased to 40, 27, and 27, respectively, while the total score decreased to 17.2. Thus while initially reported as severe, significant improvement in severity and impact of symptoms occurred over time.

Since the time of initial presentation, the patient began dietary supplementation with 5HTP/L-tryptophan, magnesium, vitamin B12, Lion's Mane, and Gingko Biloba as possible ways of alleviating the tinnitus. He also tried self-help sound therapy for tinnitus, which consisted of listening to high-pitched frequencies during intervals throughout the day. He reported a 10-minute period of relief from the tinnitus immediately following the cessation of the sound therapy audio. The patient also made the decision "to not be a victim [to tinnitus]" and focus on exercise, meditation, and breath work. Approximately 70 days after incident use of DMT, the patient noted that the chimes were gone and the ringing was softer. At that time the patient began experimenting with microdoses of psilocybin. The two times he had consumed this psychedelic, the tinnitus was exacerbated, and the sound of chimes returned. This effect subsided about 2 weeks afterward.

Discussion

Tinnitus is a commonly occurring condition, although there is much controversy over its etiology, with several different hypotheses (Shargorodsky, Curhan, and Farwell 2010). Multiple drugs across diverse classes have been idiosyncratically associated with tinnitus (Seligmann et al. 1996). However, we were unable to find medical literature describing cases of persistent tinnitus in response to psychedelic use.

Acute auditory phenomena are reported about half the time with DMT use (Strassman et al. 1994). Inhaled or injected DMT is sometimes associated with what users refer to as a "carrier wave" in which incredible intensity washes over the individual as the drug takes effect and sounds such as a "pinging, crackling, whirring" or even "sproing, boing" or other more cartoon-like sounds are heard. Upon a internet search using the terms "DMT and tinnitus" a few threads were discovered on forums discussing DMT use and subsequent tinnitus. One report described reproducible tinnitus that lasted several weeks, with onset of 12–48 hours after use of DMT. This user stated the sounds of tinnitus were qualitatively different than auditory phenomena associated with acute DMT use (Entranced 2017). This report mimics the timeline of onset and experiences of our patient closely. In another report, the tinnitus is described as an effect learned to be appreciated using meditation and is described as the "literal sound of creation" (Joedirt 2011). The latter report may highlight a common response in psychedelic forum threads related to tinnitus; utilizing psychological reframing and spiritual belief systems to cope with persistent tinnitus. Others have reported persistent tinnitus for months to years after DMT use or anecdotes of suicidality due to intensity of tinnitus after DMT use (Reddit 2017, 2019). Thus, development of persistent adverse effects such as tinnitus after DMT use is potentially underreported.

The Naranjo adverse drug reaction probability scale yielded a score of 5 in our patient's case suggesting that association of tinnitus with DMT use is "probable" (Doherty 2009). Of note, in calculation of the Naranjo score use of psilocybin/psilocin, which are analogues of DMT, were counted as positive rechallenge since the patient reported exacerbation of tinnitus after use of psilocybin microdoses. It is perhaps significant that our patient experienced immediate mood-enhancing and anxiolytic effects from LSD microdosing, however, over time noticed agitation for approximately 2 days after microdosing days. He then used DMT several times before the occasion, which precipitated tinnitus and had an anxiety ridden experience. Due to neuroplastic mechanisms of psychedelics as well as potential for increased neuroticism and physiological or psychological discomfort associated with microdosing, it is interesting to consider how extrapharmacological factors such as set and setting or psychological support could influence ability to tolerate microdosing or limit adverse outcomes (Anderson et al. 2019; Polito, Stevenson, and Arnone 2019).

Potential for HPPD was explored, however, the patient's presentation was not consistent with HPPD from the DSM-V or HPPD-1 or 2 from the ICD-10 (Halpern, Lerner, and Passie 2018). This is because tinnitus was chronic whereas perceptual changes from HPPD-1 are typically brief and described as a "flashback." In HPPD-2 the user experiences chronic visual changes,

however their other senses are unaffected. The patient also did not endorse conditions or symptoms of conditions that could otherwise explain persistent auditory phenomena. He also had positive responses to known treatments for tinnitus (listening to high pitched audio). However, it may be noted that the patient's psychiatric and drug use historyis consistent with postulated risk factors for HPPD (Halpern, Lerner, and Passie 2018).

The pathophysiology behind subjective tinnitus continues to be explored and debated (Haider et al. 2018). One proposed mechanism is that dysfunction of cochlear output results in reduced inhibition in the central auditory structures, thus leading to hyperactivity in the central auditory circuits (Eggermont 2008; Haider et al. 2018). The reduced cochlear output can occur as a result of cochlear ablation or selective loss of inner or outer hair cells, although may also occur via neuroplastic mechanisms (Zhao et al. 2016). Changes in the auditory structure can take hours to days (Baguley et al. 2013), a timeline that fits with the experience of the patient. Our patient had difficulty hearing around the same time of the tinnitus onset. However, the subcategory of auditory difficulties in the TFI scale (i.e., interference with hearing clearly, understanding people who are talking, and following conversation) went from 70 at presentation to 0 at follow-up.

One structure within the cochlear nucleus proposed to be involved in tinnitus generation is the dorsal cochlear nucleus (DCN), which contains a dense cluster of serotonergic fibers (Tang and Trussell 2015). Fusiform cells in the DCN possess Serotonin (5HT) 2A/2 C and 5HT7 receptors which, upon activation, cause depolarization leading to downstream excitation and enhancement of sensory input (Tang and Trussell 2015). DMT is a known agonist at 5HT2A/2 C receptors and has affinities for other 5HT receptor subtypes as well as non-serotonergic targets including ionotropic and metabotropic glutamate receptors, dopamine, acetylcholine, trace amine associated receptor (TAAR), and σ-1 receptors (Carbonaro and Gatch 2016).

Salicylate treatment is used in animal models to induce tinnitus and has been shown to pathologically activate serotonergic neurons in the Dorsal Raphe Nucleus (DRN) (Caperton and Thompson 2011). Salicylate-induced tinnitus is associated with anxiety and pretreatment with 5-MeO-DMT reduced anxiety responses associated with tinnitus in young mice (Winne et al. 2020). This may explain the paradoxical feeling of "inner peace" that the patient felt following use of DMT despite distress over development of tinnitus.

Moreover, glycine, a major inhibitory neurotransmitter in the central nervous system, executes tonic inhibition within subcortical regions (Salling and Harrison 2014). Subcortical neural circuits play a role in processing of sound perception by grouping and segregating acoustic features (Felix, Gourevitch, and Portfors 2018). Luo et al. demonstrated that in cultured auditory cortical neurons, R-2,5-dimethoxy-iodamphetamine (DOI), a psychedelic that selectively agonizes 5HT2A/2 C receptors, reversibly reduced the glycine receptor current, thus possibly contributing to central hyperexcitability (Luo et al. 2016).

Interestingly, other serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) have been reported to cause tinnitus in withdrawal, yet are sometimes used to treat tinnitus in persons affected (Clewes 2012). One proposed theory behind the utility of serotonergic agents centers around the psychiatric relief offered by the drugs rather than the alleviation of tinnitus itself (Baldo et al. 2012). Similarly, persons undergoing MDMA-assisted psychotherapy have reported coincidental reduction in tinnitus (Sessa 2015). While this is possible, it also appears more could be learned about the pathophysiology or etiologic management of tinnitus from further study of psychedelics.

Conclusion

Four months after onset of tinnitus our patient was still affected by the tinnitus, however, it is much less bothersome overall and coping with existing symptoms is adequate. Persistent neurological effects such as tinnitus are potentially underreported in medical literature and deserve additional exploration given increasing interest in use of DMT and a probable link to tinnitus.

Disclosures

Heba Diab has no conflicts of interest or disclosures.

Benjamin Malcolm provides paid psychopharmacology consultation services both to individuals and organizations seeking information about psychedelic substances.

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