Disorders due to Substance Use: Hallucinogens and MDMA-Related Substances

Sandeep M. Nayak and Matthew W. Johnson

Contents

Abstract

Hallucinogens are a broad category of substances encompassing drugs with diverse pharmacological, phenomenological, and adverse effects. In this chapter, the focus is on disorders caused by and exacerbated by two classes of hallucinogens. These are classic psychedelics (drugs including LSD and psilocybin that exert subjective effects principally by $5HT_{2A}$ agonism) and the substituted amphetamine 3,4-methylenedioxymethamphetamine

This chapter is an update from the 4th edition. Previous edition authors were Rif S. El-Mallakh, John H. Halpern and Henry David Abraham.

S. M. Nayak (✉) · M. W. Johnson
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD USA
e-mail: smn@jhmi.edu

A. Tasman et al. (eds.), *Tasman's Psychiatry*,
https://doi.org/10.1007/978-3-030-42825-9_94-1

(MDMA). In this chapter, the evidence regarding disorders and other adverse effects attributable to these drugs, including acute toxicity, abuse potential, persistent perceptual effects (Hallucinogen Persisting Perception Disorder), psychosis, neurotoxicity, and more, are explored.

Keywords

Psychedelic · MDMA · Hallucinogen · Disorders · Harm · Risks · Psychosis

Introduction

The *DSM-5* categorizes hallucinogens as a broad classification of drugs encompassing such diverse pharmacologic classes as the κ-opioid agonist salvinorin A, the anticholinergic deliriant *Datura*, the substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA), and 5-HT2A agonists – the so-called classic psychedelics. Phencyclidine (PCP) and structurally related NMDA antagonist compounds such as ketamine are specifically excluded from the category "hallucinogen" in the *DSM-5*. In *ICD-11*, "hallucinogen" includes PCP, muscimol (a $GABA_A$ agonist), and ibotenic acid (an agonist of NMDA and several metabotropic glutamate receptors), while MDMA and analogous compounds are treated separately. In our opinion, this categorization of "hallucinogen" is arbitrary, as it combines drugs that have very little shared phenomenal, pharmacologic, or clinical features. In this chapter, disorders due to classic psychedelics are discussed, and, separately, MDMA. Psychedelics are defined as drugs that exert their phenomenal effects primarily through $5HT_{2A}$ agonism and effect profound changes in perception, cognition, and affect. Structurally, these drugs are composed of psychedelics that are analogues of a tryptamine structure (e.g., psilocybin, psilocin, N,N-dimethyltryptamine (DMT), 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), and bufotenin (5-HO-DMT)), a phenethylamine structure (e.g., mescaline, 2,5-dimethoxy-4-bromophenethylamine (2C-B), 2,5-dimethoxy-4-ethylphenethylamine (2C-E)), and an ergoline structure (e.g., lysergic acid diethylamide (LSD) and lysergic acid amide (LSA)).

While MDMA does exert some effects through indirect $5HT_{2A}$ agonism, as a serotonin releaser it is pharmacologically, phenomenally, and clinically distinct enough to warrant separate discussion as a different class of drug. As classic psychedelics and MDMA have such distinctly separate mechanisms and phenomenal effects, these will be reviewed separately in turn.

In this chapter, authors have opted to take an approach that does not hew strictly to ICD and DSM classifications as it is argued that these categorizations are inadequate for the subject. These nosological systems will be referenced, but a broader approach will be taken in describing the potential risks these substances pose.

ICD-11 includes the following disorder classes: hallucinogen intoxication, dependence, harmful pattern of use, hallucinogen-induced psychotic disorder, and other specified hallucinogen-induced disorders (e.g., mood and anxiety). In contrast to *ICD-10*, *ICD-11* does not have a specifically defined category for hallucinogen persisting perception disorder. *ICD-11* has analogous disorders for MDMA. *DSM-5* recognizes the following disorder categories: hallucinogen intoxication, hallucinogen use disorder, hallucinogen persisting perception disorder, and hallucinogen-induced psychosis (Table 1).

Classic Psychedelics

Psychedelic drugs are unique compounds that tend to garner alarmist press from detractors and fanciful, grandiose claims from supporters. Across history, they have been deemed catalysts for human evolution (McKenna, 1992), tools of Satan (Masters & Houston, 1966, p. 30), the solution for world peace, and other lofty claims. Many of these assertions are grounded in the assumption that these drugs have been used for millennia by numerous cultures across the world and that they may have foundational importance for humanity. There has been fervent speculation, for example, that a variety of ancient sacramental substances – including soma/haoma of the Rig Veda and the

Table 1 Comparison of diagnoses between ICD-11 and DSM-5

	Definition of hallucinogen	Acute intoxication	Disordered use/ addiction	Psychosis	Persisting hallucinogen effects
ICD-11	Classic psychedelics, PCP, muscimol, ibotenic acid, NOT MDMA	"Hallucinogen intoxication": clinically significant, transient condition following consumption of hallucinogen that may include changes in cognition, affect, perception, behavior, and autonomic system	"Hallucinogen dependence": repeated hallucinogen use with loss of control of use, craving, use taking precedence over other important features of life, requires daily or almost daily use for 3 months. "Harmful pattern of use": a pattern of use resulting in harm to self or others	"Hallucinogen-induced psychotic disorder": psychotic symptoms (e.g., delusions, hallucinations, disorganized thinking, grossly disorganized behavior) that develop during or soon after intoxication with hallucinogen	No specific diagnosis
DSM-5	Salvinorin-A, *Datura*, MDMA, classic psychedelics, NOT PCP nor ketamine	"Hallucinogen intoxication": very similar to ICD-11	"Hallucinogen use disorder": use in greater amounts than intended, unsuccessful attempts at reducing use, excessive time spent using, obtaining, or recovering from hallucinogens, craving, tolerance, and functional impairment	"Hallucinogen-induced psychosis": clinically significant delusions or hallucinations that occur after hallucinogen use and are not better explained by another cause	"Hallucinogen persisting perceptual disorder": reexperiencing of perceptual symptoms similar to those experienced while intoxicated that are clinically impairing and not better explained by another cause

Avesta, and kykeon of the Eleusinian mysteries – may have been psychedelics. Psychedelic compounds (whether from plants, animals, or fungi) are indeed found on every continent save Antarctica, though their historically confirmed use has been confined to relatively circumscribed geographic areas – largely in the Americas. In the Americas, only two sites show definitive evidence of psychedelic use dating back millennia – Mesoamerica and the Andes. This evidence includes mescaline-containing cacti, psilocybin mushrooms, and a 5-HO-DMT and 5-MeO-DMT containing plant *Anadenanthera peregrina*. The spread of ayahuasca through the Amazon may have happened relatively recently, in post-Columbian times (Brabec de Mori, 2011).

Psychedelics exert their effects principally through $5HT_{2A}$ receptor agonism, and their subjective effects are nearly completely blocked by pretreatment with the relatively selective $5HT_{2A}$ antagonist ketanserin (Kometer et al., 2012; Valle et al., 2016; Vollenweider et al., 1998). There are a wide variety of natural and synthetic psychedelics that are commonly in use for a variety of reasons including traditional sacramental, recreational, and therapeutic.

Psychedelic mushrooms, containing the pro-drug psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) and, to a lesser extent, psilocin (4-hydroxy-N,N-dimethyltryptamine) are widely spread across the world. Psilocybin's function in fungi is not fully known, but the genes for its production have been horizontally transferred between different lineages so it likely confers some fitness value (Reynolds et al., 2018). There are dozens of psilocybin-containing

mushrooms in different genera, and the psilocybin content of these species can vary widely. Psilocybin mushrooms are typically taken orally, with onset within 60 min and effects lasting 6–8 h.

Dimethyltryptamine (DMT) is another tryptamine psychedelic that occurs in a wide range of plants with a history of traditional use centered in South America. It is taken through various routes of administration. The plant *Anadenanthera peregrina* (which contains bufotenin, 5-MeO-DMT, and DMT) is used by various Amazonian peoples as a snuff. Unlike psilocybin, its close structural cousin, DMT is not orally active. However, an Amazonian brew that is called various names including ayahuasca, yage, daime, and more contains DMT plus a reversible MAOI, allowing oral activity. Ayahuasca is typically composed of the DMT-containing plant, *Psychotria viridis* and *Banisteriopsis caapi*, a vine that contains the reversible MAOI alkaloids harmine, harmaline, and tetrahydroharmine. Other combinations of an DMT-containing plant and an MAOI are also possible. Nowadays, DMT is frequently vaporized and inhaled in its crystalline form. This method leads to onset within seconds and offset of effects within minutes.

Lysergic acid diethylamide (LSD) is perhaps the world's most famous psychedelic. This was synthesized by Alexander Hoffman who in 1943 famously ingested 250 micrograms of LSD. It is most often sold in the form of "tabs" of blotter paper upon which LSD was dropped and taken orally/sublingually. The introduction of LSD to the world led to a period of enthusiastic experimentation across different research paradigms – as a therapeutic, as a psychotomimetic, and even for its potential utility in warfare. After it gained notoriety as a recreational drug, this wave of psychedelic research ended due to a combination of social backlash and increasing regulatory difficulties.

Mescaline is perhaps the first psychedelic known to Western science and is found naturally in the peyote (*Lophophora williamsii*), San Pedro (*Echinopsis pachanoi*), and Peruvian torch (*Echinopsis peruvianus)* cacti (Jay, 2019). These cacti have longstanding traditions of use in Central and South America. Mescaline is not widely available as a synthetic drug. Apart from mescaline, there are several other naturally occurring psychedelic compounds, including 5-MeO-DMT found in the toad *Bufo alvarius* and several plants, and lysergic acid amide (LSA) found in morning glory seeds (*Ipomoea violacea*).

Several psychedelics do have an ongoing history of sacramental/religious use. The Native American Church is a syncretic Native American religious organization founded in the late nineteenth century that includes peyote rituals. These are legally allowable in the USA due to the American Indian Religious Freedom Act. Similarly, the União do Vegetal, a Brazilian ayahuasca religion, is also allowed to sacramentally take ayahuasca in the USA following a Supreme Court ruling.

There are also countless other synthetic psychedelics. The American chemist Alexander Shulgin synthesized and personally ingested hundreds of psychedelic compounds (Shulgin & Shulgin, 1991).

Common classic psychedelic drugs

Drug	Sources
Psilocybin	Various mushroom species
LSD	Synthetic, ultimately derived from ergot fungal compounds
DMT	Various plants (*Psychotria viridis*, *Mimosa tenuiflora*, *Anadenanthera peregrina*, *Anadenanthera colubrina*, *Diplopterys cabrerana*, *Acacia* species)
5-MeO-DMT	*Anadenanthera peregrina*, *Anadenanthera colubrina*, *Bufo alvarius* toad venom, *Virola elongata*
Mescaline	Peyote (*Lophophora williamsii*), San Pedro cactus (*Echinopsis pachanoi*), *Echinopsis peruvianus*

Pharmacologic Mechanisms

The prototypical phenethylamine class psychedelic is mescaline, and this class is fairly selective for $5HT_2$ receptors. Tryptamine class compounds include psilocybin and DMT and are less selective and interact with more classes of 5HT receptors,

including $5HT_1$, $5HT_6$, and $5HT_7$ (Nichols, 2004; Vollenweider & Preller, 2020). Ergoline class compounds, such as LSD, are the least specific for 5HT receptors and can bind several other receptor types. LSD is pharmacodynamically complex and partially agonizes several subtypes of $5HT_1$ in addition to $5HT_2$ (Lovenberg et al., 1993). It also exhibits $5HT_{1A}$ autoreceptor activity that suppresses serotonergic activity (Passie et al., 2008). Uniquely among commonly used psychedelics, LSD also interacts with D1 and D2 receptors (Passie et al., 2008).

The main mechanism common to all classic psychedelics is $5HT_{2A}$ agonism. This is supported by a wealth of human and animal literature. In humans, the effects of LSD, psilocybin, and DMT are blocked by the $5HT_{2A}$ antagonist ketanserin (Kometer et al., 2012; Preller et al., 2017; Valle et al., 2016; Vollenweider et al., 1998). In addition, subjective psilocybin effects are positively correlated with $5HT_{2A}$ occupancy (Madsen et al., 2019). It is still possible, however, that other $5HT_2$ subtypes play more minor roles. The $5HT_{2A}$ receptor is widely distributed throughout the cortex and found predominantly in the apical dendrites of layer 5 pyramidal neurons (Hall et al., 2000). A fuller account of the circuit-level mechanisms of psychedelics is beyond the scope of this chapter, but there may be important contributions from enhanced downstream glutamatergic transmission with possible resulting effects on neuroplasticity (Barre et al., 2016; Marek et al., 2000), as well as downstream dopaminergic effects (Vollenweider, 1999). For attempts to synthesize a global account of psychedelic effects, the interested reader is directed toward Vollenweider and Preller (2020) and Carhart-Harris and Friston (2019).

Acute Effects

Aside from receptor pharmacology, classic psychedelics are difficult to define by their effects. Grinspoon et al. (1979, p. 9) provide the following definition: "A drug which, without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis."

Psychedelics may seem to produce a bewildering variety of experiences in part because, perhaps more so than other drugs, the effects of psychedelic drugs are highly context-dependent. In the psychedelic literature, these contextual effects (both external and internal) have been termed "set and setting" effects (Hartogsohn, 2017). In the 1950s, the markedly varying effects of peyote on white research subjects compared to American Indians taking it in a culturally sanctioned sacramental setting are telling. White participants who took peyote in research settings had experiences characterized by feelings of meaninglessness, distress, "hallucinations largely idiosyncratic in content," and a general lack of therapeutic benefits (Wallace, 1959). In contrast, Native Americans taking peyote in a ceremonial setting with a presumption of a meaningful and beneficial experience enjoyed "welcome feelings of contact with a new, more meaningful… reality prefigured in doctrinal knowledge" (Wallace, 1959).

Acute Psychological Effects

Psychedelics produce a broad range of perceptual, cognitive, and affective changes (Griffiths et al., 2006, 2011). These include visual illusions (more so than hallucinations), synesthesia, an enhanced sense of meaningfulness, increased emotionality including anxiety, panic, or euphoria, alterations in sense of time (including experiences of timelessness), and alterations in the sense of self.

Psychedelics can produce very challenging, negatively valenced experiences characterized by profound fear, anxiety, dysphoria, and a distressing loss of touch with reality, all together colloquially called a "bad trip" (Carbonaro et al., 2016; Johnson et al., 2008). While non-ideal contexts seem more likely to provoke these challenging experiences, these can and do occur even among carefully screened participants in monitored clinical settings. In a psilocybin study of 18 healthy volunteers, 39% of subjects experienced extreme "fear, fear of insanity, or feeling

trapped" during their session, and 44% experienced delusions or paranoia (Griffiths et al., 2011). Notably, such challenging experiences do not preclude therapeutic benefit. Positive emotionality is also enhanced, and experiences of joy, ecstasy, and euphoria are not uncommon. Although relatively rare, without the safeguards and structure of clinical or perhaps ceremonial settings, dangerous behavior resulting from challenging experiences can result in harm including death (Carbonaro et al., 2016; Johnson et al., 2008, 2018).

The profound derangement of typical cognition and perception engendered by psychedelics inspired early researchers to study their effects as a "model psychosis." Indeed, many features of the psychedelic experience do mimic psychosis, including perceptual disturbances, paranoia, delusions, and formal thought disorder. However, it is an imperfect model. Psychedelics do not generally cause negative symptoms, for example (Gouzoulis-Mayfrank et al., 2005; Heekeren et al., 2007), and while primary psychosis is characterized by auditory more than visual hallucinations, the reverse is true for psychedelics (Bauer et al., 2011; Waters et al., 2014). Similarly, synesthesia is common under psychedelics, but not in primary psychosis (Luke & Terhune, 2013). Notably, haloperidol does not reduce psilocybin-induced visual illusions and hallucinations and in fact increases "dread of ego-dissolution," a psychometric construct encompassing dysphoric ego dissolution and derealization (Vollenweider et al., 1998).

Psychedelics can engender classical mystical experiences (Gasser et al., 2014; Griffiths et al., 2006, 2011; Stace, 1960). As described by Walter Stace, these are subjective states characterized by:

1. A sense of sacredness
2. A noetic quality: a feeling of having encountered something fundamentally true
3. Positive mood: this can include ecstasy, profound awe, peace
4. Ineffability: a sense that the experience cannot be expressed in words
5. Paradoxicality
6. Transcendence of time and space: this can include feelings of timelessness or infinite space (Stace, 1960)

One's degree of mystical experience experienced in a psychedelic trial, as operationalized by the Mystical Experience Questionnaire (Barrett et al., 2015) (whether in its 43- or abbreviated 30-item version), has been shown to be associated with various clinical outcomes, including smoking cessation, alcohol abuse, anxiety and depression associated with cancer, and major depressive disorder (Barrett et al., 2018; Bogenschutz et al., 2015; Davis et al., 2021; Griffiths et al., 2016; Johnson et al., 2014; Ross et al., 2016).

Normal Mini-Mental State Examination (MMSE) scores administered while subjects are under the influence of psilocybin suggest that typical psychedelic effects should not be understood as delirium (Barrett et al., 2018) although delirium might be an appropriate term of a subset of individuals encountered outside of clinical research.

The *DSM-5* criteria for **hallucinogen intoxication** include recent (non-phencyclidine) hallucinogen use, clinically significant behavioral or psychological changes, perceptual changes, as well as other non-specific signs including pupillary dilation, palpitations, tremors, etc. Similarly, *ICD-11* hallucinogen intoxication requires clinically significant behavioral, perceptual, etc., changes that may include a variety of features including hallucinations, illusions, paranoia, tremors, sympathomimesis, depersonalization, and more.

Ultimately, these criteria are overly broad and arguably unhelpful. This is in no small part due to lumping together substances from entirely different drug classes under the rubric "hallucinogen." The most definitive feature in diagnosing hallucinogen intoxication is history – urine toxicology for psychedelic compounds is generally not routinely available nor particularly useful. The mental status exam can mimic psychosis (hallucinations, paranoia, thought disorder), mania (euphoria, grandiose delusions, pressured

speech), and anxiety and depressed mood can be prominent. This is unlikely to present clinically except in the emergency department setting – likely for agitation, psychological distress, or bizarre behavior. The course of intoxication is highly variable and dependent on the drug – smoked DMT can last as little as minutes, whereas the effects of LSD can last 12 h. The most likely diagnostic information leading to suspicion of hallucinogen intoxication is verbal report, either spontaneously or upon inquiry, that the patient took a psychedelic. For classic psychedelics, the first treatment should be the provision of reassurance and a calming presence if possible. Otherwise, treatment should include symptomatic treatment of anxiety with benzodiazepines, and agitation with benzodiazepines and/or atypical antipsychotics. Oral diazepam is a preferred choice among benzodiazepines (Johnson et al., 2008), with dose recommendations ranging from a single 10 mg dose (Grinspoon et al., 1979) up to 15–30 mg per hour (Ungerleider & Frank, 1976). Typical antipsychotics should probably be avoided due to a potential risk for potentiating dysphoric psychedelic effects (Vollenweider et al., 1998).

Clinical Research

Psychedelics were researched for a variety of clinical conditions from the 1950s to 1970s but went into a period of dormancy, restarting in clinical settings in the 1990s and developing momentum since then. Psilocybin is the subject of several clinical studies, demonstrating preliminary promise for a variety of conditions including psychological distress associated with cancer, major depressive disorder, and tobacco and alcohol use disorders (Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Griffiths et al., 2016; Johnson et al., 2014) in fixed doses up to 25 mg or weight-based doses ranging from 20 to 30 mg/70 kg. These are moderate to high doses that are akin to or even on the higher side of recreational doses. Other psychedelics, including LSD and the DMT containing brew ayahuasca, are also being evaluated for clinical conditions (Gasser et al., 2014; Palhano-Fontes et al., 2019). This work generally excludes subjects with personal or family histories of psychosis or bipolar disorder and has demonstrated an exceptional safety profile with appropriately selected subjects and monitoring procedures.

Epidemiology of Use

The Monitoring the Future survey has surveyed US students annually since 1975. According to this survey, past year use of LSD among 8th, 10th, and 12th graders peaked in 1996 at 6.3%, declining to a nadir of 1.6% in 2013 and rising slightly to 2.2% by 2019. Past year use of the broad category "Hallucinogens other than LSD," including other classic psychedelics but also phenylcyclidine and concentrated THC, peaked in 2001 at 4.0% and subsequently declined to 1.9% in 2019 (Miech et al., 2020).

The National Survey on Drug Use and Health (NSDUH) is an annual, nationally representative survey of drug use in the USA. According to the NDUH, among the entire population age 12 and older, past year LSD use had hovered between 0.2 and 0.4% throughout the early 2000s, though it began to increase annually in 2015 to 0.9% in 2019. Among adults aged 18–25, past year LSD use was below 2% from 2002 to 2012, but then increased steadily to 3.6% in 2019. Among the entire sample, lifetime LSD use ranged from 9.6% in 2002 to 10.1% in 2018, and lifetime psilocybin use ranged from 7.9% in 2002 to 9.3% in 2018.

Toxicity

Psychedelic drugs can cause sympathetic arousal including tachycardia and hypertension (Griffiths et al., 2006, 2011). While this is generally not of clinical significance, people with significant cardiovascular conditions are usually excluded from ongoing clinical trials for this reason. There are at least a couple of reported cases of myocardial infarction from psilocybin. One was in an 18-year-old man with Wolff-Parkinson-White syndrome (Borowiak et al.,

1998). Another was in a 24-year-old woman who had received a heart transplant a decade before psilocybin use due to end-stage rheumatic heart disease (Lim et al., 2012).

Dose-dependent headaches and nausea with occasional vomiting are not uncommon following psilocybin (Griffiths et al., 2011; Johnson et al., 2012), though ayahuasca in particular may cause a greater degree of nausea and vomiting (de Lima Osório et al., 2015; Palhano-Fontes et al., 2019). Dizziness, dyscoordination, and tremors may also occur (Nichols, 2004).

Except in extreme cases such as those at severe cardiovascular risk as previously described, classic psychedelics are not known to be somatically toxic acutely or chronically, and have little potential for organ damage, even in overdose (Johnson et al., 2008; Nichols, 2004; Passie et al., 2008). Earlier research suggesting that LSD damages chromosomes appears to have been unwarranted (Bender et al., 1968,). Extrapolation from lethal doses in rodents and elephants suggests a lethal dose of LSD around 14,000 micrograms (compared to a typical dose of 100–300 micrograms), though there are no recorded human cases of death from LSD overdose. Remarkably, eight individuals who took a massive overdose of LSD intranasally (mistaking it for cocaine) and had serum LSD levels of 1000–7000 micrograms/mL survived with no long-term sequelae (Klock et al., 1975). However, all eight did require hospitalization – three required mechanical ventilation, three aspirated vomitus, and all had coagulopathy though none required blood transfusion. All left the hospital within 48 h of admission. A lethal dose of psilocybin is estimated to be 1000 times its effective dose (Gable, 2004). Thus, psychedelics are exceedingly safe. The major risk acutely is psychological distress, with potential for psychiatric decompensation subacutely.

There is also a theoretical risk of cardiac valvular disease with chronic dosing of psychedelics. Fenfluramine is a substituted amphetamine that, in combination with phentermine, was marketed as an appetite suppressant in the USA in the 1990s. The drug was pulled out from widespread circulation upon the discovery that it can cause valvular heart disease – principally aortic and mitral regurgitation and resulting in pulmonary hypertension (Palmieri et al., 2002). This effect appears to be due to $5HT_{2B}$ agonism (Rothman et al., 2000) and is similar to pathology found in carcinoid syndrome (Pellikka et al., 1993). Psychedelics, such as psilocybin and LSD, also agonize the $5HT_{2B}$ receptor and therefore may pose a similar cardiac valvular risk. While this risk is unknown, it is likely miniscule with a use pattern of moderate to large doses taken infrequently. However, one use pattern of psychedelics is microdosing, which involves low doses, sometimes taken chronically. Given $5HT_{2B}$ this may pose a cardiac risk.

Disordered Use

The *DSM-5* criteria for hallucinogen use disorder are similar to those of other drugs and include such criteria as hallucinogens used in greater amounts than intended, unsuccessful attempts at reducing use, excessive time spent using, obtaining, or recovering from hallucinongens, craving, tolerance, and functional impairment. *ICD-11* Hallucinogen Dependence criteria similarly include repeated hallucinogen use with loss of control of use, use taking precedence over other important features of life, and physiological tolerance.

Both sets of criteria are inadequate in reference to the classic psychedelics. Although use can result in harm, classic psychedelics have remarkably little evidence of compulsive use potential that is presumed by many of the criteria, and psychedelic use is typically devoid of the usual hallmarks of disordered drug use, including dependence, withdrawal, craving, and escalating use in the face of mounting drug-related consequences (Johnson et al., 2018; Nichols, 2004). Rhesus macaques do not reliably self-administer psilocybin, mescaline, or DMT (Fantegrossi et al., 2004). Cohen (1960) received questionnaire data from 44 researchers (70% of those contacted replied) who had administered LSD or mescaline to patients or healthy volunteers, encompassing nearly 5000 individuals dosed over 25,000

sessions. No instances of addiction to LSD were reported.

Tolerance to $5HT_{2A}$ agonists, however, develops rapidly, with cross-tolerance across drugs including psilocybin, LSD, and mescaline (Abramson et al., 1956, 1960; Wolbach et al., 1962). Tolerance can occur after a single dose such that an identical dose the following day barely produces threshold effects (Abramson et al., 1956). Tolerance is also rapidly lost, over the course of days. The mechanism of this is presumably due to receptor downregulation, which has been demonstrated in rodents (Buckholtz et al., 1985).

DMT may be the exception to this. DMT, perhaps uniquely among known psychedelics, does not appear to produce tolerance when administered IV in humans (Strassman et al., 1996). Animal data also suggest a lack of both tolerance formation (Gillin et al., 1973; Kovacic & Domino, 1976) and cross-tolerance with other tryptamine psychedelics (Kovacic & Domino, 1976). In humans, intramuscular DMT is active in LSD-tolerant individuals (Rosenberg et al., 1964). In contrast, LSD is cross-tolerant with psilocybin and mescaline in humans (Isbell, 1959; Wolbach et al., 1962). The mechanism for DMT's unique tolerance profile is unclear. It is noteworthy that chronic serotonergic antidepressants (including MAOIs) may block the effects of psychedelics – it is unknown whether this is mediated through the same signaling mechanisms as tolerance (Bonson et al., 1996; Grof & Dytrych, 1965; Gukasyan, 2023).

Despite such rapid and profound tolerance for most psychedelics, these drugs do not cause physical dependence. There has been no reported withdrawal phenomenon, and large doses of psychedelics are in fact often followed by an "afterglow" – a pleasant, non-impairing state characterized by positive mood that can last weeks to a month (Majić et al., 2015).

Preliminary evidence suggests psychedelics may have potential to treat other addictions, including tobacco smoking (Johnson et al., 2014), alcohol abuse (Bogenschutz et al., 2015), and opioid addiction (Savage & McCabe, 1973), though there has been no definitive study to date. Naturalistic psychedelic use may also lead to reductions in misuse of alcohol and other drugs although the causal nature of the association is not certain (Garcia-Romeu et al., 2019, 2020).

Psychosis Related to Psychedelics

Diagnostic Criteria

The criteria for hallucinogen-induced psychosis in the *DSM-5* are identical to those for any substance/medication-induced psychotic disorder, and include the presence of clinically significant delusions or hallucinations that occur after hallucinogen use and are not better explained by another cause. *ICD-11* criteria are nearly identical.

This designation is unfortunately tautological and can elide the presence of an underlying affective or primary psychotic disorder. Modern clinical psychedelic studies generally exclude prospective participants with a history of psychosis or bipolar disorder, and sometimes even people with a first-degree family history of these. This reflects an awareness that psychedelics may exacerbate or unmask these disorders. While psychedelics may certainly cause psychosis in individuals without an active underlying disorder, there is a risk in reflexively viewing psychosis precipitated by a psychedelic as "hallucinogen-induced psychosis" without considering the possibility of "hallucinogen-induced exacerbation of an underlying psychotic disorder."

Literature Review of Psychosis Cases

Below is reviewed what is known about the risk of psychosis with psychedelics. Most of these studies are older, so there is the relevant caveat that American psychiatric nosology in the 1950s–1970s was heavily biased toward schizophrenia to the relative exclusion of manic depression (Cooper et al., 1969). Thus, it is unfortunately difficult to distinguish the two from a historic diagnosis.

Of Cohen (1960)'s questionnaire of researchers encompassing 5000 patients and subjects dosed with LSD or mescaline, there were eight episodes of psychosis lasting longer than 48 h. The only one that occurred in a

non-therapeutic research setting involved the identical twin brother of an individual with schizophrenia. He received 180 mcg IV LSD and 2 days later developed anxiety and depersonalization requiring a 5-day hospitalization. He was treated with barbiturates and discharged in good condition after 5 days.

Seven other cases in this sample involved prolonged psychosis in therapeutic settings. Two made a complete recovery within weeks, whereas the remaining five had either chronic or unclear courses. These include a 23-year-old depressed man with prior "hallucinatory experiences" who "barricaded himself into a room and made an abortive suicidal attempt. The psychotic manifestations persisted for a fortnight and was terminated with 48 hours of deep sleep therapy." Another experienced a "chronic LSD state for weeks, culminating in an undifferentiated schizophrenic reaction," requiring hospitalization and treatment with phenothiazines. He is noted to have made a slow, but complete recovery over 6 months. Another patient was a man who developed hyper-religiosity and anxiety in his late 20s–early 30s. He was treated with successive doses of LSD and developed psychosis requiring hospitalization. He had slow recovery over a year and a half. From this sample, an incidence of 0.08% of prolonged psychosis is noted in non-therapeutic experimental subjects and 0.18% in therapy subjects (Cohen, 1960).

Baker (1964) reported on 150 inpatients with "functional psychiatric disorders" treated with LSD 100–2000 micrograms per session for 1–10 sessions. Of these, 4/150 (2.7%) developed psychoses that required termination with ECT. While not strong evidence, their resolution with ECT raises suspicion for affective psychoses. Two of the four had previous psychotic episodes with recovery. Notably, other patients in this sample with prior psychoses did not develop psychosis, but no number is mentioned.

Ungerleider et al. (1966) reviewed psychiatric emergency room records involving LSD over a 7-month period encompassing 70 patients. Of these 27% had previous outpatient psychiatric care, though diagnoses are not clear. Twenty-five (36%) were hospitalized, and 12 (17%) required hospitalization longer than a month.

Fink et al. (1966) administered LSD 60 micrograms–250 micrograms to 65 inpatients. They are all described as having a history of psychosis, though it is not clear from description why they were hospitalized at the time of study. Out of 158 administrations, three (2%) led to prolonged reactions. It is striking that in a sample of patients with psychotic disorders, all three cases appear consistent with manic depressive illness.

The first case involved a 20-year-old man with one prior episode of "bizarre behavior. . . destructiveness, manic excitement," paranoia, and hallucinations who received three successive doses of LSD leading to euphoria, lability, and delusions of guilt that resolved over 3.5 months of treatment with trifluperidol.

The second case was a 25-year-old man with 4 years of negative symptoms with a cyclic course that responded to drug treatment. After LSD 40 micrograms, he developed paranoia and depersonalization. He threw himself out of the car on a home visit the following day and became increasingly depressed, expressing a desire to die. Over the course of a week, he developed euphoria, "uncontrollable giggling," and decreased sleep. He was discharged in improved, but not resolved, condition after 8 months of inpatient antipsychotic treatment.

The final case was a 48-year-old man with cyclic episodes of depression alternating with euphoria, aggression, inappropriate laughter, as well as persecutory delusions and hallucinations. His first dose of LSD 70 micrograms led to no change in symptoms while on trifluperidol therapy. A second dose – LSD 60 micrograms administered after tapering trifluperidol – led to aggression, elation, flight of ideas, and auditory hallucinations. He received chlorpromazine 200 mg IM but continued to have manic and psychotic symptoms. Over the course of 2.5 months of antipsychotic treatment, he improved to the point of discharge.

Other sources from which to ascertain risk include groups that sacramentally use psychedelics. Bergman (1971) estimated a rate of one

psychotic reaction per 70,000 peyote ingestions among a population of 30,000 Native American Church members assumed to have an average session every 2 months. This was an intentional overestimate that, with the obligatory caveat about demographic confounds, is reassuring from a risk perspective. The União do Vegetal, a Brazilian ayahuasca religion, maintains an epidemiologic surveillance system for psychiatric disorders among its users. From 1994 to 2007, there were 29 psychotic occurrences, including 4 manic episodes with psychosis, and 4 major depressive episodes with psychosis, though these were not well characterized (Lima et al., 2011). In 19/29 cases, ayahuasca was determined to be the main contributing factor. Four cases had no prior psychiatric history. Lima et al. (2011) estimate 130,000 person-years of UDV membership from 1994 to 2007 and determine (based on risk in the general Brazilian population) 20.5 (95% CI[18.6, 22.9]) expected cases of psychosis per 130,000 person-years. In the UDV sample, the 29 psychosis cases per 130,000 person-years suggest that ayahuasca may contribute to greater psychosis risk in susceptible people, though there are several potential confounds. Other population studies do not show an association of psychedelic use with greater mental health problems when controlling for other relevant variables (Hendricks et al., 2015), including primary psychosis and mania (Krebs & Johansen, 2013).

There are several case reports that are generally difficult to interpret given many confounds (such as concurrent use of other drugs), but two are worth mentioning. Szmulewicz et al. (2015) reported on a 30-year-old man with prior hypomania and a father with bipolar I disorder, who developed mania 2 days after ayahuasca consumption.

dos Santos and Strassman (2011) report the case of a 21-year-old man with no known family or personal psychiatric history save 6 years of near-daily cannabis use. He had been using ayahuasca roughly twice a month for 2 years (with near-daily cannabis) when during an ayahuasca ceremony he acutely developed paranoid delusions which persisted for 2–3 weeks and resolved with risperidone. A year later, he resumed ayahuasca without risperidone or cannabis. After his third session, he developed a similar psychotic episode. He ceased ayahuasca use though used LSD, psilocybin, and MDMA without issue in the interim. He developed a similar psychotic episode after an ingestion of MDMA, and again after 2C-I (2,5-dimethoxy-4-iodophenethylamine) (dos Santos et al., 2017). If it is assumed these psychoses were indeed triggered by these drug experiences (which is not clear), it can be concluded that the risk of psychosis in a susceptible individual is not uniform – most drug sessions did not induce psychosis in this patient.

Notably, in the hundreds of administrations of psilocybin administrations at Johns Hopkins, there have been no provocations of psychosis or mania, suggesting that potential risks of psychosis and mania can be mitigated in appropriately screened people. To our knowledge, at other research sites in the USA, the UK, Switzerland, Spain, and Brazil, there have been no instances of psychosis or mania occasioned by experimental psychedelic administration to carefully screened participants.

Summary

Key questions are whether psychedelics pose differential risks for people with primary psychotic and bipolar diatheses, whether and how this risk can be mitigated, and whether different drugs pose different risks. There is unfortunately not enough information to answer these questions. Erring on the side of caution, some reasonable conclusions can nevertheless be drawn:

1. Psychedelics pose a relatively low risk of triggering psychosis in appropriately screened people.
2. They likely can exacerbate primary psychotic disorders and bipolar disorders in predisposed people (with a personal or family history), and such people are especially advised to avoid them.
3. The risk of psychedelics in bipolar II disorder is not clear.
4. It is unknown whether different psychedelics pose different risks.

5. It is unknown whether psychosis and mania risk can be mitigated with medications or other interventions.

Hallucinogen Persisting Perception Disorder (HPPD)

Introduction

Sandison and Whitelaw (1957) make perhaps the first reference to LSD recurrence phenomena: LSD "is liable to produce a repetition of the acute phase of the experience days or even weeks after the initial doses. It is probable that repeated and larger doses of LSD produce the most severe and prolonged after-effects, but this phenomenon is seen well marked in patients who have had no more than 50 mcg weekly."

Colloquially called psychedelic "flashbacks," the condition of post-psychedelic hallucinatory phenomena remains vaguely defined in prevalence and subjective characteristics. Because the categorizations of this condition in *DSM-5*, *ICD-10*, and the case report literature differ significantly, and because it is the subject of immense controversy and confusion in the public sphere, an overview of the concept, its history, its phenomenology, and different categorization schemes is provided.

Diagnosis

Comparison of *ICD*/*DSM* Diagnostic Criteria

ICD-11 does not have specific criteria for HPPD. However, *ICD-10* (Organization, 2004) includes the following two codes related to HPPD: **F16.283 hallucinogen dependence with hallucinogen persisting perception disorder (HPPD) (flashbacks)** and **F16. 983 Hallucinogen use, unspecified with hallucinogen persisting perception disorder (flashbacks).** It is specified that "Flashbacks may be distinguished from psychotic state partly by their episodic nature, frequently of very short duration, and by their duplication of previous alcohol- or other psychoactive substance-related experiences." Notably, these two definitions do not entirely converge. In contrast, *DSM-5* Hallucinogen Persisting Perception Disorder (HPPD) criteria include the reexperiencing of perceptual symptoms similar to those experienced while intoxicated that are clinically impairing and not better explained by another cause.

Lerner et al. (2014) delineate two types of post-psychedelic flashback syndromes, one of which does not neatly fit within the *DSM-5* criteria. Here their categorization is borrowed as it is useful for organizing the literature. The two types share phenomenology but are distinguished in chronicity and severity. Type I is milder, intermittent, and more transient than type II and may fit better with the *ICD-10* classification. Type II HPPD is similar to type I but more severe, enduring, functionally impairing, and distressing, and coheres better with *DSM-5* criteria. The two conditions can likely be understood as lying on a spectrum of severity.

Diagnosis of HPPD is fairly straightforward following *DSM-5* criteria though largely encompasses what is described as HPPD II above. The major diagnostic considerations involve ruling out other causes. These include ophthalmologic causes and organic CNS pathology (including tumors, neurodegenerative disorders, head trauma, drug toxicities, stroke, seizure disorder, etc.). Distinction from psychotic disorders is also necessary but straightforward.

An important caveat to bear in mind is that the majority of information about HPPD comes from case reports and are subject to all their attendant biases. While it is difficult to infer causality from case reports, it is prudent to err on the side of caution and do so anyway when dealing with a potentially serious adverse effect.

Type I HPPD

Type I HPPD could likely be simply termed psychedelic "flashbacks" – intermittent recurrences of psychedelic-like phenomenon that are largely benign. These can be defined as "transient spontaneous recurrences, usually multiple, of certain aspects of the psychedelic drug effect occurring after a period of relative normalcy following the original intoxication" (Shick & Smith, 1970).

A typical description is offered by Horowitz (1969): "Sometimes the sidewalk seems to bend as if it's going downwards – even when I'm not on

anything – or it just kinda vibrates back and forth." Flashbacks appear to be primarily visual (illusions, pseudohallucinations, and hallucinations) but can include a range perceptual and affective changes. These may occur without any clear prompting, days, months, or even years after last hallucinogen use. They may range from amusing to distressing (McGlothlin & Arnold, 1971). Vague somatic symptoms as well as derealization, depersonalization, or a dream-like quality to reality may be present. Insight is retained with all these experiences. Because HPPD I is generally not functionally impairing and is self-limited, it may often not lead to clinical presentation. A survey of 235 LSD users found that 28% reported experiencing flashbacks; 36% found these experiences disruptive and 16% sought clinical help (Naditch & Fenwick, 1977). Flashbacks are felt to be provoked by stress, other substances (especially cannabis (Halpern et al., 2018)), hypnagogia, dark environments, or volition, but also to occur spontaneously.

Abraham (1983)'s report of 123 subjects with LSD exposure recruited from a psychiatric emergency service details a variety of visual phenomena that can occur with HPPD. They described symptoms included color confusion, difficulty reading, phosphenes, geometric pseudohallucinations, illusions of movement, halos around objects, palinopsia (visual trails that follow moving objects), and intensified colors. Other types of symptoms include aeropsia (visual snow), fragmentation of objects, pointillist visualizations, distorted distance perception, and pareidolias (Lerner et al., 2014).

Notably, those symptoms are distinct from psychosis. In a study of schizophrenia patients with HPPD, 8/12 (67%) patients reported that HPPD symptoms were distinguishable from psychotic hallucinations (Lev-Ran et al., 2014).

Type II HPPD

Type II HPPD is more severe, chronic, and distressing and entails "constant or near-constant visual effects" (Halpern et al., 2018). Per Lerner et al. (2014), "The principal difference between these two conditions rests on the patient's perception of impairment and disability. HPPD I is perceived as a benign pleasant state whereas HPPD II is perceived as a severe, unpleasant state." Rosenthal first described this type of prolonged post-psychedelic reaction "lasting as long as 6 months or more after the last drug experience. The hallucinations are marked by their similarity to those experienced while under the influence of the drug itself. Both pleasant and frightening effects are seen. The frightening hallucinations are involuntary. Cats, crabs, insects, corpses and the skulls of familiar people are among the things that have been reported. The pleasant sensations are semi voluntary in the sense that the subject can make them more or less intense to the extent that he concentrates on them. They consist characteristically of the breakup of light into droplets of color, shimmering panels of color before the patient's eyes and brightly colored shape distortions. Hallucinosis may also be accompanied by fear and panic" (Rosenthal, 1964).

Distinguishing HPPD I and HPPD II

HPPD I	HPPD II
Intermittent, transient episodes	Chronic, persistent
Mild	More severe
Generally non-impairing	Functionally impairing
Less likely to present clinically	More likely to present clinically

Epidemiology

Studies of HPPD vary greatly in estimates of prevalence, which partly reflects differing definitions. Earlier reports were notable for a relative absence of reports on HPPD. Smart and Bateman (1967)'s review of the literature found only 11 cases of recurrent LSD-like experiences. In contrast, Horowitz (1969) estimated 1 in 20 users would have at least a mild form of flashback. Similarly, in a Los Angeles County Survey of Health Professionals, Ungerleider et al. (1968) reported that 26% of survey respondents indicated that over half of their LSD patients experienced flashbacks.

In a follow-up survey of 247 people who had received LSD in experimental or psychotherapeutic settings, McGlothlin and Arnold (1971) reported 14.6% indicated they had experienced some kind of spontaneous recurrence of LSD-like symptoms. By and large, these were mild and transient and would fit with HPPD I. Only 1 case of 36 patients experiencing flashbacks was significantly distressing.

A survey of 2256 enlisted army members found 88 who experienced flashbacks (as defined by the respondent) that they attributed to one or two drugs. A majority of flashbacks (54.5%) were attributed (by the subjects) to LSD (Stanton & Bardoni, 1972). Only 5% of flashbacks were attributed to amphetamines and 1% to cannabis.

Abraham (1983) reported 53.5% of subjects with a history of LSD use recruited through an emergency psychiatry service endorsed flashbacks. These were fairly enduring, and 12.9% of these subjects had sought clinical help.

Krebs and Johansen (2013) argue that visual disturbances are common among the general population and that the long duration between psychedelic intake and symptom onset argues against causality. It remains unclear to what extent healthy subjects who have not taken psychedelics have HPPD-like symptoms and to what extent psychedelic flashbacks may lie on a spectrum of non-pathological, transient, unusual sensory experiences. Abraham (1983) found a mean of 4.8 ± 3.0 HPPD-type visual symptoms in a sample with HPPD compared to 1.8 ± 3.0 in healthy controls.

Schankin et al. (2013) reported on 57 patients who endorsed "persistent, dynamic, black & white tiny dots in the entire visual field," termed visual snow, or aeropsia. A majority of subjects also reported excessive visual floaters (also termed *mouches volantes*; 84%), persistent afterimages (83%), palinopsia (56%), and phosphenes (51%). These subjects denied any use of illicit drugs prior to symptom onset. However, if they had taken a hallucinogen prior to symptom onset, it is likely they would have met criteria for HPPD. Interestingly, 54% of these subjects had a history of migraine.

Studerus et al. (2011) pooled data from eight psilocybin dosing studies totaling 110 subjects, 90 of whom completed long-term follow-up questionnaires. Of these 90, 10% endorsed experiencing spontaneous altered states of consciousness prior to receiving psilocybin, 9% endorsed such states after, and 3.3% endorsed such states both before and after. These experiences could not be distinguished from each other and were generally found to not be impairing. Only 3.3% of subjects endorsed visual alterations, which were mild. These were infrequent, transient, and largely appeared in relation to darkness, hypnagogia, meditation, and so on. Similarly, a sample of 80 members of the Native American Church who had taken peyote at least 100 times found no cases of HPPD (Halpern et al., 2005). It may be that properly selected patients in supportive settings are less likely to develop HPPD.

A subset of an online psychedelic survey, which comprised 174 people who had taken LSD, psilocybin, MDMA, cocaine, ketamine, and alcohol, showed that 22% responded "definitely yes" to reexperiencing psychedelic drug effects (Carhart-Harris & Nutt, 2010). A majority (55%) felt LSD to be most responsible.

Clinical Issues

Course

Much of what is known about HPPD comes from case studies, which are blunt-objects that have limitations in understanding the natural history of a disorder. HPPD I may arise quickly or gradually. There is no certainty about the dose required to elicit HPPD. Cohen and Ditman (1963) report onset of HPPD after a single dose of LSD. Abraham (1983) showed a dose-response relationship that peaks at 15 and 40 lifetime doses of LSD and thereafter plateaus, and McGlothlin and Arnold (1971) found that flashbacks were more common in individuals who had 10 or more exposures. Other research is conflicting, both showing a dose-response relationship (Naditch & Fenwick, 1977) and not (Stanton & Bardoni, 1972). It appears there is great variability, though it is

sensible to believe that more exposure leads to greater risk.

Strassman (1984) notes that psychedelic flashbacks "are usually self-limited and diminish in duration, intensity, and frequency with time," and this is echoed by other authors (Horowitz, 1969; Lerner et al., 2014; Shick & Smith, 1970). In contrast, the patients described in Abraham (1983) (mentioned above) had symptoms that were durable over time, did not dissipate, and were functionally impairing – all more in keeping with HPPD II and the *DSM-5* criteria. In general, it appears that symptoms are generally paroxysmal and mild, but can also be severe, chronic, and enduring. The distinction between HPPD I and II usefully partitions these two courses, though it is unlikely these are fundamentally different processes.

Comorbidity

Diagnosing comorbid affective and anxiety disorders, which may be more common in this population, is key. While not captured by existing diagnostic schema, it is likely helpful to categorize people into HPPD I (transient, self-limited) versus HPPD II (chronic, persistent).

Etiology and Pathophysiology

Various explanations have been offered to explain HPPD symptoms, including psychodynamic formulations (Horowitz, 1969; Naditch & Fenwick, 1977), disinhibition of visual pathways (Abraham, 1983), and exacerbation of preexisting hypersensitivity to low-level visual information (Halpern et al., 2018).

Abraham (1983) suggests HPPD may be due to a failure to inhibit low-level visual noise. This could occur through damage to or otherwise altered function of 5-HT2A expressing cortical inhibitory interneurons (Litjens et al., 2014). Similarly, Carhart-Harris and Friston (2019) propose that, acutely, psychedelics relax visual priors that normally constrain perception such as "walls don't breathe." Under relaxed visual priors, low-level visual noise is unconstrained and can make conscious appearance as breathing walls or bending sidewalks. If a similar mechanism were to persist, HPPD could conceivably result. To date, there is no data to confirm or refute chronic relaxation of perceptual priors following psychedelic experiences.

This conjecture is made more plausible by the existence of non-drug-induced conditions wherein a circumscribed sensory experience durably alters subsequent sensory experience. *Mal de débarquement* is a rare vestibular disorder that idiosyncratically develops after passage on a ship or airplane (or even sleeping on a waterbed (Murphy, 1993)), constituting a persistent rocking, swaying, or bobbing sensation after returning to land. It can be debilitating and has few treatment options. It may be understood as perceptual learning that generates inappropriate, enduring perceptual priors.

Halpern et al. (2018) performed a survey that recruited individuals with persistent perceptual disturbances after any triggering event, not just drug use. One individual with no prior history of drug use endorsed symptoms that were indistinguishable from HPPD II. They suggest the possibility that HPPD is due to preexisting over-activation of visual pathways that becomes a self-reinforcing focal point of anxiety after a psychedelic experience. This may explain why cases of HPPD seem more often attributed to distressing psychedelic experiences (Halpern et al., 2018; Lev-Ran et al., 2014; Naditch & Fenwick, 1977). They suggest that "HPPD may be an anxiety disorder not unlike PTSD, where the triggering drug experience is the traumatic event." The same study suggests that people with a family history of anxiety, complaints of tinnitus, visual floaters, and poor concentration may be more prone to developing HPPD II.

Descriptions of HPPD and flashbacks appear similar to visual experiences that may occur during migraine aura, including seeing "polygonal latticeworks" or "gridding" or "mosaic-vision" with fragmentation reminiscent of a pointillist painting (Sacks, 1992, p. 278). It is unclear whether migraine is a risk factor for HPPD, though Litjens et al. (2014) did not find a relationship. It is noteworthy that HPPD-like visual symptoms (palinopsia) can be an acute adverse effect of other serotonergic drugs, including trazodone (Hughes & Lessell, 1990), risperidone

(Lauterbach et al., 2000), and mirtazapine (Ihde-Scholl & Jefferson, 2001). This bolsters the probability that classic psychedelics, as serotonergic agents, do in fact cause HPPD. However, it is also worth mentioning that other drugs are associated with flashbacks, including ketamine (Abraham & Salzman, 2017), cannabinoids (Halpern et al., 2018; Lerner et al., 2011), and MDMA (see below) (Litjens et al., 2014). It is possible that psychedelics are more commonly associated with flashbacks than other drugs because of a true greater risk of causing flashbacks. However, it is also possible, because of this common association, flashbacks are attributed to psychedelics rather than other drugs or preexisting conditions. Other classic psychedelics apart from LSD, including mescaline and psilocybin, have also been associated with HPPD, though there are fewer reports of these (Halpern et al., 2018). Transient recurrence of drug-like effects following 5-MeO-DMT may be particularly common, though these are mostly positively valenced (Ortiz Bernal et al., 2022). Nonetheless, it is impossible to say whether different psychedelics carry different risks for inducing HPPD.

Ultimately, these speculations are not mutually exclusive and may in fact be complementary. Whether through bottom-up overactivity or top-down disinhibition, it seems plausible that HPPD results in part from excitatory and inhibitory imbalance in the visual system.

Treatment

There is no definitive treatment for HPPD, but a variety of case reports have been published. Risperidone and phenothiazine antipsychotics appear to exacerbate HPPD symptoms (Abraham, 1983; Morehead, 1997), though there are conflicting reports. A single case study showed benefit with 0.5 mg risperidone (Subramanian & Doran, 2014). Similarly, a case study of trifluoperazine in an individual with constant palinopsia and other intermittent visual phenomena revealed a few days of worsened palinopsia followed by improvement (Anderson & O'Malley, 1972). Intermittent flashback symptoms, however, did not improve. This pattern of transient worsening followed by improvement may hold true for other neuroleptics. One case showed worsening with 5 mg olanzapine but subsequent improvement on risperidone 2 mg and sertraline 150 mg (Espiard et al., 2005). Similarly, a different case demonstrated initial worsening with risperidone but improvement with olanzapine and fluoxetine (Aldurra & Crayton, 2001). Both these cases included SSRIs, which have discordantly shown improvement (Young, 1997) and worsening of visual symptoms (Markel et al., 1994). A small study of haloperidol in eight patients found increased flashbacks for the first week with a subsequent decrease that was not statistically significant (Moskowitz, 1971).

Benzodiazepines appear helpful (Lerner et al., 2003; Abraham, 1983), as does clonidine (Lerner et al., 2000).

Lerner et al. (1997) report two cases of naltrexone resolving HPPD symptoms with durable benefit after discontinuation. Two cases showed great improvement with lamotrigine 200 mg after 13 years (Hermle et al., 2012) and 18 years of visual symptoms (Hermle et al., 2013) which were severe enough to impair reading and attributed to LSD. Notably, a retrospective chart review of treatment for visual snow (which phenomenologically overlaps significantly with HPPD) showed that 5/26 patients (19.2%) experienced partial remission with lamotrigine – more so than any other treatment (Dongen et al., 2019).

Of course, it is unclear to what extent the effect of any of these treatments is attributable to spontaneous remission. While there is no well-evidenced treatment for HPPD, lamotrigine may be a good first option given its favorable safety profile.

Special Factors Influencing Treatment

There are no general statements that can be made regarding special factors influencing the treatment of hallucinogen related disorders given the very broad expanse of drugs included under the rubric of hallucinogen.

Summary

Erring on the side of caution, it is reasonable to conclude that recurrences of psychedelic-type experiences are possible, may be not uncommon,

but are generally benign and self-limited. Some may go on to develop a more persistent and enduring course of visual aberrations accompanied by distress, though this appears to be rare, and it is not clear what factors predispose to this. Lamotrigine is a reasonable first choice for treatment in those with persistent, disturbing symptoms.

MDMA

MDMA is the shorthand for methylenedioxymethamphetamine, a substituted amphetamine first synthesized in 1912 by Merck as a chemical intermediate of a compound to stem abnormal bleeding. While it is considered a "hallucinogen" under *DSM-5* categorization, its mechanism and effects are substantially different than classic psychedelics. Moreover, MDMA poses significantly greater acute and chronic risks over classic psychedelics.

In the 1920s, MDMA was briefly studied as a vasoconstrictor, but research did not proceed further. It escaped notice for decades until the US military began testing it on animals in the 1950s as part of a larger program to develop aides to interrogation, but this research program also did not progress (Pentney, 2001).

Alexander Shulgin resynthesized MDMA in 1965, and this became the dominant synthesis to this day. Prior to this, the mescaline derivative methylenedioxyamphetamine (MDA) – an analogue of MDMA – was in use as a psychotherapy adjunct. The psychoactive effects of MDA were discovered by Alles in 1930 via self-experiment (Jay, 2023) in the late 1950s, and the Chilean psychiatrist Caudio Naranjo began studying it in the early 1960s as a psychotherapy adjunct. Although a mescaline derivative, MDA was favored for psychotherapy due to its ability to intensify emotions and insights, with less overt psychedelic effects (Passie, 2018). MDA was banned in 1970, which likely accelerated a turn to MDMA as a psychotherapy adjunct. Alexander Shulgin tested MDMA on himself in 1976 and subsequently began distributing it to psychotherapists (Passie, 2018). Its use in psychotherapy was predicated on its ability to enhance feelings of connection and reduce defensiveness (McDowell & Kleber, 1994).

MDMA's mainstream use started first in psychotherapy and later spread to recreational use. While recreational MDMA use may have occurred as early as 1968, it did not really expand until the late 1970s and especially the 1980s (Siegel, 1986). A longitudinal analysis of street drugs between 1972 and 1985 found no MDMA prior to 1975, with MDMA positive samples gradually increasing until surpassing MDA in the 1980s (Renfroe, 1986).

MDMA is often adulterated. In the late 1980s, when MDMA made its recreational debut under the moniker "Ecstasy," the drug was generally pure (Parrott, 2004). MDMA remained unscheduled, largely out of media attention, and was even able to be freely purchased at bars in Texas. Its increasing use eventually provoked public outrage, and it was added to schedule I in 1985. Nonetheless, demand increased, though by the early 1990s the drug was increasingly adulterated.

Perhaps in recognition of this, the moniker "Molly" – short for "Molecular," indicating unadulterated, crystalline MDMA – emerged (Palamar, 2017). This name has become meaningless, however. A US study found that only 63% of samples contained MDMA or an analogue, with the most common adulterant being DXM (Baggott et al., 2000). A sample of 150 drug seizures by police in Brazil found MDMA in only 44.7% of samples – methamphetamine and caffeine were the next most common drugs (Togni et al., 2015). Of 529 samples from musical events throughout the USA, only 60% of samples contained MDMA or MDA at all; the presence of MDMA was unrelated to naming such as "Molly" or "ecstasy" (Saleemi et al., 2017). The most common adulterants were cathinones ("bath salts") and methamphetamine. Users may not be aware that they are taking other drugs. While the most common adulterants may change over time, adulteration has been relatively common over decades. Still, it is possible that purity has increased since the nadir in the 1990s.

Pharmacologic Mechanisms

MDMA binds presynaptic monoamine transporters, particularly SERT, but also DAT, and leads to massive efflux of serotonin and – similar to amphetamines – dopamine and norepinephrine, albeit to a lesser extent than serotonin (Gouzoulis-Mayfrank & Daumann, 2006; Liechti et al., 2001). It is a substituted amphetamine that bears some structural similarity to mescaline and can be thought of as an amphetamine with unique serotonergic properties that produces some phenomenal effects akin to psychedelics as well as unique empathogenic effects. Indeed, the $5HT_{2A}$ antagonist ketanserin attenuates some of the perceptual effects of MDMA, but not its main effects of positive mood, wellbeing, and extroversion (Liechti et al., 2001; Liechti & Vollenweider, 2000). Therefore, from a risk consideration, MDMA overlaps significantly with other amphetamines but poses its own risks. Strikingly, a blind study comparing PO methamphetamine and MDMA showed that participants experienced with both drugs were unable to reliably distinguish them (Kirkpatrick et al., 2012). Haloperidol, a selective D2 antagonist, reduces MDMA's euphorigenic effect, but does not impact visual alterations, cardiovascular changes, or adverse effects broadly (Liechti et al., 2001). Notably, citalopram, an SSRI which inhibits SERT, blocks the majority of subjective MDMA effects when given acutely (40 mg IV) (Liechti & Vollenweider, 2000).

Oral MDMA reaches peak concentration 2–4 h after administration. However, MDMA exhibits nonlinear pharmacokinetics such that higher doses lead to disproportionately higher concentrations (De La Torre et al., 2000). This may be because MDMA is metabolized by CYP2D6 but also inhibits it. Thus, if a single dose of MDMA is split and administered as two separate doses, the split dose leads to higher concentrations (Peiró et al., 2013). This suggests that caution should be exercised when MDMA is taken with other CYP2D6 inhibitors such as fluoxetine or bupropion.

Reboxetine, a selective norepinephrine transporter inhibitor, reduces the cardiovascular effects of MDMA, including heart rate, blood pressure, and serum norepinephrine (Hysek et al., 2011). Bupropion similarly reduces MDMA-induced elevations of heart rate and serum norepinephrine despite increasing serum MDMA levels and prolonging its subjective effects (perhaps due to CYP2D6 inhibition) (Schmid et al., 2015).

Acute Effects

In the *DSM-5*, MDMA intoxication is categorized under the same criteria for Other Hallucinogen Intoxication, as above. However, as a distinct drug from a distinct drug class, it has different clinically relevant effects to be aware of.

Positive Acute Effects

Positive acute effects of MDMA include feelings of empathy, closeness, euphoria, increased alertness, and increased visual luminescence (Passie, 2018; Peroutka et al., 1988; Verheyden et al., 2003). MDMA's effectiveness in reducing fear, enhancing empathy, and interpersonal closeness led to its use in couple's therapy. The American psychiatrist Rick Ingrasci who treated many couples with MDMA described its effects as "It puts a person in an unbelievable open frame of mind... the expanded capacity for self-awareness, the increased ability to share feelings. All that's attributable... to the lowered fear and anxiety induced by this drug" (Ingrasci, quoted in Passie (2018)).

Adverse Acute Effects

Adverse effects include typical amphetamine effects including tachycardia, insomnia, diaphoresis, tremor, palpitations, anorexia, anxiety, as well as trismus and bruxism. MDMA can also induce SIADH, which in combination with advice to "drink plenty of water" while dancing all night has led to fatal hyponatremia (Moritz et al., 2013). This risk appears to be greater in females (Moritz et al., 2013).

MDMA can also cause hyperthermia on the order of 0.2–0.8 °C in controlled settings (Liechti, 2014) and more in individuals who are dancing in clubs (Parrott & Young, 2014). This may occur

through a noradrenergic mechanism involving metabolic generation of heat coupled with cutaneous vasoconstriction (Liechti, 2014). This is dose dependent, and there are reported fatalities due to this (Liechti, 2014). The treatment is as any other case of hyperthermia. Notably, the drug para-methoxymethamphetamine, a common adulterant of MDMA, seems to be particularly likely to cause hyperthermia, and this has caused fatalities (Lurie et al., 2011).

MDMA's sympathomimetic effects via noradrenergic mechanisms can lead to elevated blood pressure (Mas et al., 1999), as well as cardiotoxicity including arrythmias and myocardial infarctions (Badon et al., 2002). Chronically, as an indirect 5HT2B agonist, MDMA may also cause cardiac valvulopathy with heavy, regular use (Droogmans et al., 2007).

As a serotonergic drug, MDMA can cause serotonin syndrome, so caution must be taken with drugs that agonize serotonin, especially MAOIs, which can be fatal (Vuori et al., 2003).

Clinical Research

In recent years MDMA has been studied as a treatment for PTSD and has thus far shown promise in several controlled trials for this indication when administered as an adjunct to therapy (Mithoefer et al., 2011, 2018). As of late 2020, it is in phase III trials for PTSD, though there are trials for other indications including anxiety associated with cancer and social anxiety in autism (Danforth et al., 2018).

Epidemiology of Use

In 2014, high school seniors endorsed 8.0% lifetime and 5.1% 12-month use of MDMA (Palamar et al., 2016). According to the 2018 National Survey on Drug Use and Health (NSDUH), 7.4% of all respondents endorsed ever taking MDMA. Annual MDMA use in young adults increased from 0.8% in 1991 to 2.9% by 1998. Annual use then peaked in 2001 (7.5% among young adults) and subsequently declined to 3.7% in 2018. In 2019, 13.2% of 19–28-year-olds endorsed lifetime MDMA use (Schulenberg et al., 2020). MDMA is typically used infrequently and by individuals in their twenties (Smirnov et al., 2013). Nonetheless, it remains common in some subcultures, including the Electronic Dance Music scene (Palamar et al., 2017).

The typical MDMA user uses intermittently, about one to two tablets of roughly 70–120 mg each (Gouzoulis-Mayfrank & Daumann, 2006; McDowell & Kleber, 1994; Pantoni & Anagnostaras, 2019; Verheyden et al., 2003). A smaller fraction of people takes more doses per occasion more frequently. Perhaps because MDMA depletes brain serotonin stores, repeated doses of the drug in a session eventually lead to diminishing returns (McDowell & Kleber, 1994). This may partially explain its intermittent use pattern. Of surveyed MDMA users, only 13–17% had used 100 times or greater (Parrott et al., 2006; Scholey et al., 2004), only 9–17% of users take 3–4 doses per session, and only 3–10% take more than doses 4 per session (Pantoni & Anagnostaras, 2019). This typical use pattern of intermittent dosing is important to bear in mind in reviewing human studies of long-term MDMA effects below.

Laboratory animals do reliably self-administer MDMA (Fantegrossi et al., 2004; Schenk, 2009), but in humans, MDMA addiction (including physiological dependence, tolerance, escalating use in spite of consequences) appears to be rare. There are some indications that the positive effects of MDMA decrease overtime while negative ones increase (Peroutka et al., 1988). Moderate use of MDMA is common and may be the norm (Peroutka et al., 1988; Von Sydow et al., 2002; Wu et al., 2008). A longitudinal study of German 14–24 year olds showed that of subjects meeting criteria for *DSM-IV* ecstasy dependence, 93% were no longer dependent at 3 year follow-up, and 50% were no longer using the drug at all. The majority of MDMA users in this sample did not meet criteria for abuse or dependence at baseline, and the majority of these were no longer using at follow-up (Von Sydow et al., 2002). In the 2005 NSDUH, 3.6% of MDMA users met

criteria for *DSM-IV* dependence, and 4.9% met criteria for *DSM-IV* abuse (Wu et al., 2008).

Cottler et al. (2009) recruited 593 participants from three sites who had used ecstasy more than five times in their lifetime and performed a computerized assessment of drug use patterns. They reported that 59% met criteria for *DSM-IV* dependence and 15% met criteria for *DSM-IV* abuse. Regarding dependence, a majority of users endorsed withdrawal, continued use despite knowledge of physical or psychological problems from it, whereas a minority endorsed using more than intended, persistent desire to cut down, or giving up important activities due to MDMA use. In a separate sample of non-treatment seeking MDMA users, a relatively large portion (25.8%) reported $\geq$3 *DSM-IV* dependence symptoms – more so than users of cocaine, ketamine, and mephedrone (Uosukainen et al., 2015). However, MDMA users were less likely to endorse persistent desire to take MDMA or a desire to cut down use. This is in keeping with the typical sporadic use pattern of MDMA. These high rates of dependence with intermittent use are in conflict and are likely an artifact of procrustean DSM criteria that are not appropriate for this drug. Especially given the typical, intermittent use pattern of MDMA, it is likely these reports of withdrawal and use despite knowledge of physical or psychological problems reflect the "comedown" rather than true dependence (McKetin et al., 2014).

Neurotoxicity

Animal Evidence

It is absolutely clear from a variety of nonhuman animal studies that, at some dose and/or frequency, MDMA causes long-term alterations in serotonergic activity, as measured by levels of 5HT, its metabolite 5-hydroxyindoleacetic acid (5-HIAA), and SERT. It is also likely (though less clear) that similar long-term alterations in serotonergic function may occur in humans with heavy use. It remains unclear whether typical, moderate use of MDMA in humans can lead to such changes.

In a since retracted paper, Ricaurte et al. (2002) mistakenly administered IV methamphetamine rather than MDMA to five squirrel monkeys and found dopaminergic damage. The paper was retracted after Ricaurte discovered and reported the error. This retraction garnered a great deal of publicity and cast undue doubt on other, more established facts of MDMA toxicity. There does not appear to be clear evidence that MDMA causes dopaminergic damage, but long-term serotonergic alterations are well established.

Due to differences in metabolism and distribution, there is some controversy in how to compare animal dosing of MDMA to humans. Typical recreational human doses are 1–2 tablets of 75–125 mg each (roughly 1–3 mg/kg) (Pantoni & Anagnostaras, 2019). Similarly, ongoing MDMA therapeutic trials for PTSD use up to a 125 mg dose, with an optional supplemental dose 50% of the original (Mithoefer et al., 2011, 2018). The majority of MDMA animal studies demonstrating neurotoxic or adverse cognitive effects use interspecies dose-scaling equations that lead to markedly higher "equivalent" doses – on the order of 10–20 mg/kg (Battaglia et al., 1987; Pantoni & Anagnostaras, 2019; Schmidt, 1987).

The rationale behind interspecies dose scaling is that smaller animals require higher doses due to differences in drug elimination. However, going by behavioral threshold effects, a 1–2 mg/kg PO dose in humans is thought to produce equivalent effects as a similar dose – delivered intraperitoneally or subcutaneously – in rats (Baumann et al., 2007). Similarly, equivalent weight-based doses in humans and rats lead to prolactin and glucocorticoid secretion and reinforcement (Mas et al., 1999,). If, as this evidence suggests, equivalent weight-based doses are in fact equivalent between humans and rats, then the majority of studies demonstrating rat neurotoxicity use doses vastly beyond equivalent typical human doses.

Animal studies that use human-equivalent weight-based doses are less likely to show neurotoxicity. Baumann et al. (2007) administered a dosing regimen of placebo vs 1.5 mg/kg MDMA vs 7.5 mg/kg MDMA intraperitoneally three times over 6 h to Sprague-Dawley rats. Two weeks later,

rats who received high-dose MDMA had persistent, selective reductions (~50%) of 5HT in frontal cortex and striatum, while the lower dose (more typical of human recreational dosing) did not differ from placebo (Baumann et al., 2007). Similarly, high- (10 or 15 mg/kg IP), but not low-dose MDMA (4 mg/kg IP) caused long-term 5HT depletion in rats (O'hearn et al., 1988).

In squirrel monkeys, interspecies dose-scaling equations were used to calculate doses equivalent to typical human doses of 1.6, 2.8, and 4.0 mg/kg. This resulted in doses of 5.7, 10.0, and 14.3 mg/kg, administered as single doses (Mueller et al., 2013). This study showed that all doses led to reductions in 5HT, 5-HIAA, and/or SERT in multiple brain regions measured a week later.

As in the example of rats above, interspecies dose-scaling procedures can be inaccurate. To address this, M. Mueller et al. (2013) assessed drug concentrations, which were compared to previous pharmacokinetic data comparing humans and squirrel monkeys. A dose in squirrel monkeys of 5.7 mg/kg produces a similar AUC to a human dose of 1.6 mg/kg (3866 ± 891 ng/ml.h vs 3071 ± 673 ng/ml.h in humans). However, Cmax values are substantially different at these doses (724 ± 255 ng/ml vs 254 ± 60 ng/ml). In contrast, a dose of 2.8 mg/kg in squirrel monkeys produces a similar Cmax to a 1.6 mg/kg dose in humans (254.7 ± 60.4 vs 312.7 ± 92.8) (Mueller et al., 2009, 2013). Depending on the pharmacokinetic parameter, these are difficult to compare. Further complicating this evidence is interspecies differences in brain vs plasma concentrations of substituted amphetamines. For example, brain concentrations of fenfluramine in rats are 30–50 times higher than plasma versus <10 in humans (Baumann et al., 2007).

In rats, MDMA administration causes delayed loss of 5HT axon terminals (Molliver et al., 1990; O'hearn et al., 1988). This can be mitigated by administering an SSRI as late as –6 h after an MDMA dose (Schmidt, 1987; Shankaran et al., 1999). Notably, some users take an SSRI as the effect of MDMA is wearing off to prevent the "crash," though it is unclear how this practice originated and there is no empirical evidence for its utility in humans (Koslow, 2020).

Human Evidence

There is also evidence for enduring alterations in serotonergic function in humans. While this data is largely associational in high-dose users – erring on the side of caution and taking into account the clear concordance with monkey and rat data – it is reasonably convincing.

Kish et al. (2010) showed lower SERT binding throughout the cortex in MDMA users (n = 49; age = 26; median 126 lifetime tablets [SD 31]) relative to controls(−19% to −46%) with striatal sparing. Another PET study showed similar results in a population with median 50 lifetime MDMA sessions and mean age 31 (Urban et al., 2012). These subjects had a median 0.8 uses a month. This study also demonstrated an association of decreased SERT availability with MDMA use.

McCann et al. (2005) demonstrated lower SERT binding in MDMA users (n = 23; 97 mean lifetime doses; aged 22) versus (n = 19) controls. SERT binding was correlated with duration of abstinence and inversely correlated with typical monthly dose, suggesting dose-response and recovery effects. Other cross-sectional studies in humans suggest decreased SERT binding may be reversible (Thomasius et al., 2003).

Heavy MDMA users have lower CSF levels of the serotonin metabolite 5-HIAA (McCann et al., 1994, 1999). Decreased SERT may lead to compensatory upregulation of $5HT_{2A}$ receptors (Benningfield & Cowan, 2013; Urban et al., 2012).

Overall, it appears reasonable to conclude that, at some dose, MDMA can cause altered serotonergic function. The dose required for this, and whether that includes modest recreational or therapeutic use, is still not entirely clear. A review of 19 imaging studies of individuals with moderate MDMA use (defined as <50 lifetime episodes of use or < 100 lifetime tablets consumed) found no differences controls in structural MRI, fMRI, FDG-PET, nor SERT density and $5HT_{2A}$

availability measured by PET and SPECT (Mueller et al., 2016). The functional consequences of MDMA-associated serotonergic alterations are also not fully clear. Furthermore, whether such alterations in serotonergic function reflect cell damage is unclear. Nonetheless, there are demonstrable neuropsychological deficits associated with MDMA use.

Neuropsychological Consequences

Deficits of verbal memory are associated with long-term MDMA use (Back-Madruga et al., 2003; Reneman et al., 2000; Thomasius et al., 2006; Verbaten, 2003). Brain $5HT_{2A}$ cortical density in abstinent MDMA users (mean lifetime number of tablets 218 [range 50–500]) compared to controls was correlated with deficits in verbal memory (Reneman et al., 2000). Back-Madruga et al. (2003) showed no difference between MDMA users and controls on a variety of neuropsychological tests with the exception of poorer verbal memory.

Verbal memory deficits are apparent in more moderate users as well. In an innovative prospective study of 188 MDMA naive subjects who were considering MDMA use in the near future, subjects underwent neuropsychological testing and completed questionnaires about their drug use every 3 months for 18 months (Schilt et al., 2007). Three years later, they again underwent neuropsychological testing. Of the 158 subjects who completed the study, 64 (41%) reported taking MDMA with a mean of 3.2 tablets. Verbal learning and memory were impaired in the incident MDMA group. This same cohort demonstrated persistently altered neuroimaging findings (de Win et al., 2008). These included decreased metrics of cerebral blood flow in the basal ganglia and altered fractional anisotropy in the thalamus, frontoparietal white matter, and the globus pallidus – indicating effects on microvasculature and potentially axonal integrity. However, there were no changes in SERT density. Minimal prospective MDMA use in this group was not associated with increased depression or impulsivity. In contrast, a purely correlational study of modest MDMA users (mean 44.1 total tablets) showed greater impulsivity by self-report and behavioral tasks (Morgan, 1998). This is, of course, subject to obvious confounds.

A systematic review of observational studies demonstrated deficits in attention, memory (particularly verbal and working memory), executive functioning, and self-rated depression and anxiety (Rogers et al., 2009). These effects were, in aggregate, small with the exception of verbal memory.

Halpern et al. (2004) used a unique sample of MDMA users (median total 60 doses [range 31–110]) with minimal use of other drugs. This study assessed a variety of neurocognitive measures and found no statistically significant differences between the MDMA group and a non-MDMA using controls. When the MDMA group was divided into moderate users (22–50 lifetime uses; $n = 12$) and heavy users (60–450 uses; $n = 11$), heavy users showed poorer mental processing speed and strategic self-regulation compared to controls. This persisted after controlling for several demographic variables.

Wunderli et al. (2017) demonstrated deficits in declarative memory with primary MDMA use, with more significant and nonspecific deficits in executive function and working memory appearing to be related to use of other drugs. MDMA use is associated with impairments in attention (Gouzoulis-Mayfrank et al., 2000; McCann et al., 1999) and executive function (Bhattachary & Powell, 2001; Fisk & Montgomery, 2009). Similarly, a sample of moderate (though note this is considered heavy in other studies) MDMA users (mean total 93.4 doses [range 20–500]) displayed impairments in attention, memory, and learning relative to two controls (Gouzoulis-Mayfrank et al., 2000).

Mood

MDMA acutely causes euphoria, but in the days after dosing leads to transient low mood, a phenomenon well-known to MDMA users and termed “Suicide Tuesday,” among other names (Verheyden et al., 2002; Verheyden et al., 2003,). While it is reasonable to speculate that this results

from circumstances of the drug's use – such as sleep deprivation, dancing for hours, etc. – this effect does occur in laboratory studies as well (Liechti et al., 2001; Vollenweider et al., 1998).

Whether MDMA causes chronic depression is less clear. Associational studies suggest this, but confounds including reverse causation and contributions of poly-drug use mean this is unknown [de Win et al., 2004;]. One study found no relationship after controlling for use of other drugs (Roiser & Sahakian, 2004). Notably, another found that higher depression scores in MDMA users are unrelated to SERT availability (de Win et al., 2004). A 2-year longitudinal sample of MDMA users with mean 36.2 and median 11.2 lifetime uses found decreasing Beck Depression Inventory scores (BDI) at each time point in both continued MDMA users and abstainers. In sum, the human data do not clearly suggest one way or another whether MDMA contributes to depression.

Psychosis

Like other amphetamine analogues, MDMA can provoke psychosis in predisposed people. There is debate about whether amphetamine-induced psychosis should be understood as a distinct psychotic disorder, or as a stressor in a stress-diathesis model in individuals already predisposed to psychosis (Bramness et al., 2012). As an amphetamine analogue, it is relevant to turn to the amphetamine psychosis literature to try to understand the psychosis risk that MDMA might pose.

Bell (1973) administered IV methamphetamine in escalating doses to 16 subjects with a goal of provoking psychosis. Four subjects could not tolerate higher doses due to nausea and vomiting. All remaining 12 became psychotic upon reaching an adequate dose that varied widely between subjects. One subject required 640 mg to experience psychosis, though for the remainder, a range of 55–260 mg was sufficient to induce psychosis. This was characterized by paranoia and hallucinations without thought disorder – mostly lasting 1–2 days. Notably, all these subjects were amphetamine dependent. A similar study using escalating daily doses of PO amphetamine induced psychosis in 4/4 people (Griffith et al., 1968). These were all amphetamine experienced individuals, who became psychotic after maximum daily doses 100 mg, 120 mg, 200 mg, and 220 mg, respectively. Dosing was terminated at the onset of paranoia.

In general, amphetamine-induced psychosis is indistinguishable from that of schizophrenia, though there tends to be less thought disorder and it tends to resolve quicker (Bramness et al., 2012). However, these are not hard and fast rules. A sample of 39 female Japanese prisoners with a history of methamphetamine-induced psychosis included 20 who experienced recurrence of psychosis in the absence of stimulants. This was verified by serological testing during those episodes. Eight of these had persistent psychosis, lasting for more than 6 months. In the case of these recurrences of psychosis without drugs, perhaps it is more sensible to say that methamphetamine unmasked an underlying psychotic diathesis. Patients with schizophrenia are in fact more prone to developing psychosis after amphetamines (Lieberman et al., 1987). Moreover, methamphetamine users who develop psychosis are five times more likely to have relatives with schizophrenia than methamphetamine users without a psychosis history (Chen et al., 2005).

So both models appear to be true. Unlike with classic psychedelics, an adequate dose of amphetamine appears to be able to make nearly anyone psychotic – what can truly be called amphetamine-induced psychosis. However (and as with psychedelics) they can also provoke psychosis in individuals with an underlying predisposition to it.

While extrapolating psychosis risk from other amphetamine analogues to MDMA appears reasonable, it is unclear whether MDMA poses a greater or lesser risk.

Creighton et al. (1991) reported a case of a man who took MDMA 4–7 times a week over 4 months and presented with paranoid delusions, thought disorder, and bizarre behavior. He was discharged without intervention, did use cannabis, and had resumption of symptoms 2 months later. He was treated to resolution with antipsychotics and upon

ceasing, had another similar episode after taking MDMA. No mention is made of personal or subsequent psychiatric history nor family history. They also relate two cases involving hyper-religious/paranoid delusions during the effect of the drug, followed by intermittent visual illusions accompanied by anxiety. These latter symptoms are not clearly psychotic and may be more in line with HPPD, and HPPD symptoms have been reported after MDMA use (Halpern et al., 2018; Mcguire et al., 1994).

McGuire and Fahy (1991) report on a man with prior amphetamine-induced psychoses and a mother with schizophrenia who developed paranoid delusions after taking MDMA (2–10 tablets on weekends for 1.5 years). These symptoms responded to haloperidol though later recurred with no drug use.

Another case involved an 18-year-old man who smoked cannabis regularly for 5 months then developed prolonged psychosis after taking 4 half tablet doses of MDMA on separate occasions over a 1 month period (Williams et al., 1993). Other cases are similar (Mcguire et al., 1994; Patel et al., 2011; Potash et al., 2009; Vaiva et al., 2001).

Overall, there is less evidence regarding the psychosis risk of MDMA compared to other amphetamine analogues. Again erring on the side of caution, the safest assumption is that MDMA poses an at least equivalent psychosis risk as other amphetamine analogues.

Clinical Vignette 1

An 18-year-old female college student with a family history of bipolar 1 disorder in her father, and a personal history of a single episode of major depression is brought by family to the ED with 1 week of behavior change after taking LSD for the first time.

Her speech is tangential, difficult to make sense of, but unpressured. She donated her entire paycheck the day before to a political campaign and has newly made plans to become a nun. Her mother reports she has had trouble sleeping. She reports her mood as "excellent."

She is admitted voluntarily and treated with olanzapine monotherapy to her baseline. No sleep disruption is noted throughout the admission. She is diagnosed with substance-induced psychotic disorder, though schizophreniform disorder and bipolar disorder remain on the differential.

She remains in outpatient care for 6 months and is then lost to follow-up.

Three years later, she returns to the ED with a chief complaint of "anxiety" in the setting of studying for finals.

She is initially calm, albeit bizarre, and when offered olanzapine screams "I don't need a fucking antipsychotic!" and begins screaming about a variety of other topics of clear paranoid content. Collateral from her family indicates that she has been posting about conspiracy theories on social media at all hours of the day and has apparently not slept for several days. She quit her job 3 days ago, believing that she has millions of dollars in savings.

She accepts PO lorazepam and is agreeable to a voluntary admission. Further history confirms no intake of drugs since before her prior hospitalization, but an intervening period of depressed mood with suicidal ideation. She is treated with lithium and PRN lorazepam to baseline and discharged on lithium monotherapy with a provisional diagnosis of bipolar 1 disorder.

This vignette indicates that the boundaries between substance-induced psychotic disorders, primary psychotic disorders, and bipolar 1 disorder are often unclear, particularly at first presentation. While many of the drugs discussed in this chapter can likely provoke psychosis, this should raise suspicion for an underlying primary psychotic or affective disorder – particularly in individuals with a first-degree family history of same.

Clinical Vignette 2

A 25-year-old male is brought in by police for bizarre behavior. He was found wandering the city barefoot in winter weather, talking about "dream people."

On presentation, he is dressed inappropriately for the cold weather in a t-shirt, pants, and is barefoot. He has several shallow lacerations and abrasions on his palms, elbows, and soles.

His speech is of normal rate, volume, and prosody and is unpressured and interruptible. However, he does not respond appropriately to questioning, stating "You are just a dream person." He talks to himself with content focused on "dream people" and "God" and "Enlightenment," with thought process intermittently exhibiting flight of ideas and tangentiality. He frequently closes his eyes and lies back on the bed, ignoring questions.

Stated mood is "I think you are Zapdos," and affect is labile – intermittently euphoric, crying and neutral.

He is not able to respond to basic orientation questions other than his name. Insight and judgment are poor.

He has his cellphone in his possession with dozens of missed calls. Collateral from his roommates indicates that they, as a group, had each taken 5 g of dried *Psilocybe cubensis* mushrooms and gone to a local art museum. He occasionally drinks modest quantities of alcohol but has no other history of substance use including psychedelic drugs prior to today.

The patient and his roommates were escorted out of the museum due to the patient touching paintings. Upon leaving, the patient animatedly began talking about "dream people" and sprinted away, falling several times. His roommates were not able to calm him, and he escaped and thereafter did not respond to their phone calls. They report that the patient has no psychiatric history other than a single depressive episode that was successfully treated with psychotherapy in the past year.

He is intermittently fearful and anxious but responds to frequent orientation and reassurance by nursing staff.

Over the course of 2 h, he becomes more appropriate, responsive, and develops insight that he is under the effects of a drug. He states that he feels "weird" and describes perceptual abnormalities ("walls breathing. . . close-eyed visuals. . ") but no true hallucinations in any modality.

After three more hours, he has a normal mental status exam and is discharged into the care of his roommates.

This vignette demonstrates a typical clinical presentation of acute psychedelic intoxication. The major acute risks are from dangerous behaviors that may result from the intoxicated state and can be mitigated by a safe and supportive environment. The patient in this vignette responded to reassurance and time, though in the event of agitation that cannot otherwise be de-escalated, benzodiazepines (as described above) or atypical antipsychotics may be used.

References

Abraham, H. D. (1983). Visual phenomenology of the LSD flashback. *Archives of General Psychiatry, 40*(8), 884–889.

Abraham, H. D., & Salzman, C. (2017). Hallucinogen persisting perception disorder following therapeutic ketamine: A case report. *Journal of Alcoholism & Drug Dependence, 5*(281), 2.

Abramson, H. A., Jarvik, M. E., Gorin, M., & Hirsch, M. (1956). Lysergic acid diethylamide (LSD-25): XVII. Tolerance development and its relationship to a theory of psychosis. *The Journal of Psychology, 41*(1), 81–105.

Abramson, H. A., Rolo, A., Sklarofsky, B., & Stache, J. (1960). Production of cross-tolerance to psychosis-producing doses of lysergic acid diethylamide and psilocybin. *The Journal of Psychology, 49*(1), 151–154.

Aldurra, G., & Crayton, J. W. (2001). Improvement of hallucinogen-induced persistent perception disorder by treatment with a combination of fluoxetine and

olanzapine: Case report. *Journal of Clinical Psychopharmacology, 21*(3), 343–344.

Alles, G. A. (1959). Some relations between chemical structure and physiological action of mescaline and related compounds. In H. Abramson (Ed.), *Neuropharmacology* (pp. 181–268). Josiah Macey Jr. Foundation.

Anderson, W., & O'Malley, J. E. (1972). Trifluoperazine for the trailing phenomenon. *JAMA, 220*(9), 1244–1245.

Back-Madruga, C., Boone, K. B., Chang, L., Grob, C. S., Lee, A., Nations, H., & Poland, R. E. (2003). Neuropsychological effects of 3,4-Methylenedioxymethamphetamine (MDMA or ecstasy) in recreational users. *The Clinical Neuropsychologist, 17*(4), 446–459. https://doi.org/10.1076/clin.17.4.446.27939

Badon, L. A., Hicks, A., Lord, K., Ogden, B. A., Meleg-Smith, S., & Varner, K. J. (2002). Changes in cardiovascular responsiveness and cardiotoxicity elicited during binge administration of ecstasy. *Journal of Pharmacology and Experimental Therapeutics, 302*(3), 898–907.

Baggott, M., Heifets, B., Jones, R. T., Mendelson, J., Sferios, E., & Zehnder, J. (2000). Chemical analysis of ecstasy pills. *JAMA, 284*(17), 2190–2190.

Baker, E. (1964). The use of lysergic acid diethylamide (LSD) in psychotherapy. *The Canadian Medical Association Journal, 91*, 1200–1202.

Barre, A., Berthoux, C., De Bundel, D., Valjent, E., Bockaert, J., Marin, P., & Bécamel, C. (2016). Presynaptic serotonin 2A receptors modulate thalamocortical plasticity and associative learning. *Proceedings of the National Academy of Sciences, 113*(10), E1382–E1391. https://doi.org/10.1073/pnas.1525586113

Barrett, F. S., Johnson, M. W., & Griffiths, R. R. (2015). Validation of the revised mystical experience questionnaire in experimental sessions with psilocybin. *Journal of Psychopharmacology, 29*(11), 1182–1190. https://doi.org/10.1177/0269881115609019

Barrett, F. S., Carbonaro, T. M., Hurwitz, E., Johnson, M. W., & Griffiths, R. R. (2018). Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: Effects on cognition. *Psychopharmacology, 235*(10), 2915–2927. https://doi.org/10.1007/s00213-018-4981-x

Battaglia, G., Yeh, S., O'Hearn, E., Molliver, M. E., Kuhar, M. J., & De Souza, E. B. (1987). 3, 4-methylenedioxymethamphetamine and 3, 4-methylenedioxyamphetamine destroy serotonin terminals in rat brain. *Journal of Pharmacology and Experimental Therapeutics, 242*, 911–916.

Bauer, S. M., Schanda, H., Karakula, H., Olajossy-Hilkesberger, L., Rudaleviciene, P., Okribelashvili, N., Chaudhry, H. R., Idemudia, S. E., Gscheider, S., Ritter, K., & Stompe, T. (2011). Culture and the prevalence of hallucinations in schizophrenia. *Comprehensive Psychiatry, 52*(3), 319–325. https://doi.org/10.1016/j.comppsych.2010.06.008

Baumann, M., Wang, X., & Rothman, R. (2007). 3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: A reappraisal of past and present findings. *Psychopharmacology, 189*, 407–424.

Bell, D. S. (1973). The experimental reproduction of amphetamine psychosis. *Archives of General Psychiatry, 29*(1), 3540. https://doi.org/10.1001/archpsyc.1973.04200010020003

Bender, L., Sankar, D. S., Irwin, S., & Egozcue, J. (1968). Chromosome damage not found in leukocytes of children treated with LSD-25. *Science, 159*(3816), 749–749.

Benningfield, M., & Cowan, R. L. (2013). *Brain serotonin function in MDMA (ecstasy) users: Evidence for persisting neurotoxicity* (Vol. 38). Nature Publishing Group. https://doi.org/10.1038/npp.2012.178

Bergman, R. L. (1971). Navajo peyote use: Its apparent safety. *American Journal of Psychiatry, 128*(6), 695–699.

Bhattachary, S., & Powell, J. H. (2001). Recreational use of 3, 4-methylenedioxymethamphetamine (MDMA) or 'ecstasy': Evidence for cognitive impairment. *Psychological Medicine, 31*(4), 647.

Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P. C. R., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Psychopharmacology, 29*(3), 289–299. https://doi.org/10.1177/0269881114565144

Bonson, K. R., Buckholtz, J. W., & Murphy, D. L. (1996). Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. *Neuropsychopharmacology, 14*(6), 425–436. https://doi.org/10.1016/0893-133X(95)00145-4

Borowiak, K. S., Ciechanowski, K., & Waloszczyk, P. (1998). Psilocybin mushroom (psilocybe semilanceata) intoxication with myocardial infarction. *Journal of Toxicology: Clinical Toxicology, 36*(1–2), 47–49.

Brabec de Mori, B. (2011). *Tracing hallucinations – Contributing to a critical ethnohistory of ayahuasca usage in the peruvian amazon* (B. C. Labate, & H. Jungaberle, Eds.). LIT-Verlag.

Bramness, J. G., Gundersen, Ø. H., Guterstam, J., Rognli, E. B., Konstenius, M., Løberg, E. M., Medhus, S., Tanum, L., & Franck, J. (2012). Amphetamine-induced psychosis – A separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry*, 12. https://doi.org/10.1186/1471-244X-12-221

Buckholtz, N. S., Freedman, D. X., & Middaugh, L. D. (1985). Daily LSD administration selectively decreases serotonin2 receptor binding in rat brain. *European Journal of Pharmacology, 109*(3), 421–425. https://doi.org/10.1016/0014-2999(85)90407-8

Carbonaro, T. M., Bradstreet, M. P., Barrett, F. S., MacLean, K. A., Jesse, R., Johnson, M. W., & Griffiths, R. R. (2016). Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *Journal*

of Psychopharmacology, 30(12), 1268–1278. https://doi.org/10.1177/0269881116662634

Carhart-Harris, R., & Friston, K. (2019). REBUS and the anarchic brain: Toward a unified model of the brain action of psychedelics. *Pharmacological Reviews, 71*(3), 316–344. https://doi.org/10.1124/pr.118.017160

Carhart-Harris, R., & Nutt, D. (2010). User perceptions of the benefits and harms of hallucinogenic drug use: A web-based questionnaire study. *Journal of Substance Use, 15*(4), 283–300.

Carhart-Harris, R., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *The Lancet Psychiatry, 3*(7), 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7

Chen, C. K., Lin, S. K., Sham, P. C., Ball, D., Loh, E. W., & Murray, R. M. (2005). Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *American Journal of Medical Genetics – Neuropsychiatric Genetics, 136 B*(1), 8791. https://doi.org/10.1002/ajmg.b.30187

Cohen, S. (1960). Lysergic acid diethylamide: Side effects and complications. *The Journal of Nervous and Mental Disease, 130*(1), 30–40.

Cohen, S., & Ditman, K. S. (1963). Prolonged adverse reactions to lysergic acid diethylamide. *Archives of General Psychiatry, 8*(5), 475–480.

Cooper, J. E., Kendell, R. E., Gurland, B. J., Sartorius, N., & Farkas, T. (1969). Cross-national study of diagnosis of the mental disorders: Some results from the first comparative investigation. *American Journal of Psychiatry, 125*(10S), 21–29.

Cottler, L. B., Leung, K. S., & Abdallah, A. B. (2009). Test–re-test reliability of DSM-IV adopted criteria for 3, 4-methylenedioxymethamphetamine (MDMA) abuse and dependence: A cross-national study. *Addiction, 104*(10), 1679–1690.

Creighton, F. J., Black, D. L., & Hyde, C. E. (1991). 'Ecstasy' psychosis and flashbacks. *British Journal of Psychiatry, 159*(Nov), 713–715. https://doi.org/10.1192/bjp.159.5.713

Danforth, A. L., Grob, C. S., Struble, C., Feduccia, A. A., Walker, N., Jerome, L., Yazar-Klosinski, B., & Emerson, A. (2018). Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: A randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology, 235*(11), 3137–3148.

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of psilocybin-assisted therapy on major depressive disorder: A randomized clinical trial. *JAMA Psychiatry, 78*(5), 481–489.

De La Torre, R., Farré, M., Ortuño, J., Mas, M., Brenneisen, R., Roset, P. N., Segura, J., & Cami, J. (2000). Non-linear pharmacokinetics of MDMA ('ecstasy') in humans. *British Journal of Clinical Pharmacology, 49*(2), 104–109. https://doi.org/10.1046/j.1365-2125.2000.00121.x

de Lima Osório, F., Sanches, R. F., Macedo, L. R., dos Santos, R. G., Maia-de-Oliveira, J. P., Wichert-Ana, L., de Araujo, D. B., Riba, J., Crippa, J. A., & Hallak, J. E. (2015). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: A preliminary report. *Revista Brasileira de Psiquiatria, 37*(1), 13–20. https://doi.org/10.1590/1516-4446-2014-1496

de Win, M. M. L., Reneman, L., Reitsma, J. B., Den Heeten, G. J., Booij, J., & Van Den Brink, W. (2004). Mood disorders and serotonin transporter density in ecstasy users – the influence of long-term abstention, dose, and gender. *Psychopharmacology, 173*(3–4), 376–382. https://doi.org/10.1007/s00213-003-1723-4

de Win, M. M. L., Jager, G., Booij, J., Reneman, L., Schilt, T., Lavini, C., Olabarriaga, S. D., Den Heeten, G. J., & Van Den Brink, W. (2008). Sustained effects of ecstasy on the human brain: A prospective neuroimaging study in novel users. *Brain, 131*(11), 29362945. https://doi.org/10.1093/brain/awn255

van Dongen, R. M., Waaijer, L. C., Onderwater, G. L. J., Ferrari, M. D., & Terwindt, G. M. (2019). Treatment effects and comorbid diseases in 58 patients with visual snow. Neurology, 93(4), e398–e403. https://doi.org/10.1212/WNL.0000000000007825

dos Santos, R. G., & Strassman, R. J. (2011). Ayahuasca and psychosiss. In R. G. D. Santos (Ed.), *The ethnopharmacology of Ayahuasca* (pp. 97–99). Transworld Research Network.

dos Santos, R. G., Bouso, J., & Hallak, J. (2017). Ayahuasca, dimethyltryptamine, and psychosis: A systematic review of human studies. *Therapeutic Advances in Psychopharmacology, 7*(4), 141–157. https://doi.org/10.1177/2045125316689030

Droogmans, S., Cosyns, B., D'haenen, H., Creeten, E., Weytjens, C., Franken, P. R., … & Van Camp, G. (2007). Possible association between 3, 4-methylenedioxymethamphetamine abuse and valvular heart disease. *The American Journal of Cardiology, 100*(9), 1442–1445.

Espiard, M.-L., Lecardeur, L., Abadie, P., Halbecq, I., & Dollfus, S. (2005). Hallucinogen persisting perception disorder after psilocybin consumption: A case study. *European Psychiatry, 20*(5–6), 458–460.

Fantegrossi, W. E., Woolverton, W. L., Kilbourn, M., Sherman, P., Yuan, J., Hatzidimitriou, G., Ricaurte, G. A., Woods, J. H., & Winger, G. (2004). Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys. *Neuropsychopharmacology, 29*(7), 1270–1281.

Fink, M., Simeon, J., Haque, W., & Itil, T. (1966). Prolonged adverse reactions to LSD in psychotic subjects. *Archives of General Psychiatry, 15*(5), 450–454.

Fisk, J. E., & Montgomery, C. (2009). Evidence for selective executive function deficits in ecstasy/polydrug users. *Journal of Psychopharmacology, 23*(1), 40–50.

Gable, R. S. (2004). Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction, 99*(6), 686–696.

Garcia-Romeu, A., Davis, A. K., Erowid, F., Erowid, E., Griffiths, R. R., & Johnson, M. W. (2019). Cessation and reduction in alcohol consumption and misuse after psychedelic use. *Journal of Psychopharmacology, 33*(9), 1088–1101.

Garcia-Romeu, A., Davis, A. K., Erowid, E., Griffiths, R. R., & Johnson, M. W. (2020). Persisting reductions in cannabis, opioid, and stimulant misuse after naturalistic psychedelic use: An online survey. *Frontiers in Psychiatry, 10*, 955.

Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., & Brenneisen, R. (2014). Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *The Journal of Nervous and Mental Disease, 202*(7), 513–520. https://doi.org/10.1097/NMD.0000000000000113

Gillin, J. C., Cannon, E., Magyar, R., Schwartz, M., & Wyatt, R. (1973). Failure of n, n-dimethyltryptamine to evoke tolerance in cats. *Biological Psychiatry, 7*(3), 213.

Gouzoulis-Mayfrank, E., & Daumann, J. (2006). Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: How strong is the evidence for persistent brain damage? *Addiction, 101*(3), 348–361.

Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, H. J., Fimm, B., & Sass, H. (2000). Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *Journal of Neurology Neurosurgery and Psychiatry, 68*(6), 719–725. https://doi.org/10.1136/jnnp.68.6.719

Gouzoulis-Mayfrank, E., Heekeren, K., Neukirch, A., Stoll, M., Stock, C., Obradovic, M., & Kovar, K.-A. (2005). Psychological effects of (s)-ketamine and n, n-dimethyltryptamine (DMT): A double-blind, cross-over study in healthy volunteers. *Pharmacopsychiatry, 38*(06), 301–311.

Griffith, J. J., Oates, J., & Cavanaugh, J. (1968). Paranoid episodes induced by drugs. *Journal of the American Medical Association, 205*, 39.

Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology, 187*(3), 268–283. https://doi.org/10.1007/s00213-006-0457-5

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., & Jesse, R. (2011). Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. *Psychopharmacology, 218*(4), 649–665. https://doi.org/10.1007/s00213-011-2358-5

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology, 30*(12), 1181–1197. https://doi.org/10.1177/0269881116675513

Grinspoon, L., Bakalar, J., & B.others. (1979). *Psychedelic drugs reconsidered*. Basic Books.

Grof, S., & Dytrych, Z. (1965). Blocking of LSD reaction by premedication with niamid. *Activitas Nervosa Superior, 7*(3), 306. http://www.ncbi.nlm.nih.gov/pubmed/5882136

Gukasyan, N., Griffiths, R. R., Yaden, D. B., Antoine, D. G., & Nayak, S. M. (2023). Attenuation of psilocybin mushroom effects during and after SSRI/SNRI antidepressant use. *Journal of Psychopharmacology*, 02698811231179910.

Hall, H., Farde, L., Halldin, C., Lundkvist, C., & Sedvall, G. (2000). Autoradiographic localization of 5-HT2A receptors in the human brain using [3H]M100907 and [11C]M100907. *Synapse, 38*(4), 421–431. https://doi.org/10.1002/1098-2396(20001215)38:4<421::aid-syn7>3.0.co;2-x

Halpern, J., Pope, H. G., Sherwood, A. R., Barry, S., Hudson, J. I., & Yurgelun-Todd, D. (2004). Residual neuropsychological effects of illicit 3,4- methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. *Drug and Alcohol Dependence, 75*(2), 135147. https://doi.org/10.1016/j.drugalcdep.2004.02.008

Halpern, J., Sherwood, A. R., Hudson, J. I., Yurgelun-Todd, D., & Pope, H. G., Jr. (2005). Psychological and cognitive effects of long-term peyote use among native americans. *Biological Psychiatry, 58*(8), 624–631.

Halpern, J., Lerner, A., & Passie, T. (2018). A review of hallucinogen persisting perception disorder (HPPD) and an exploratory study of subjects claiming symptoms of HPPD. *Current Topics in Behavioral Neurosciences, 36*, 333–360. https://doi.org/10.1007/7854_2016_457

Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law, 3*, 2050324516683325. https://doi.org/10.1177/2050324516683325

Heekeren, K., Neukirch, A., Daumann, J., Stoll, M., Obradovic, M., Kovar, K.-A., Geyer, M. A., & GouzouLis-Mayfrank, E. (2007). Prepulse inhibition of the startle reflex and its attentional modulation in the human s-ketamine and n,n-dimethyltryptamine (DMT) models of psychosis. *Journal of Psychopharmacology, 21*(3), 312–320. https://doi.org/10.1177/0269881107077734

Hendricks, P. S., Thorne, C. B., Clark, C. B., Coombs, D. W., & Johnson, M. W. (2015). Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *Journal of Psychopharmacology, 29*(3), 280–288.

Hermle, L., Simon, M., Ruchsow, M., & Geppert, M. (2012). Hallucinogen-persisting perception

disorder. *Therapeutic Advances in Psychopharmacology, 2*(5), 199–205.

Hermle, L., Simon, M., Ruchsow, M., Batra, A., & Geppert, M. (2013). Hallucinogen persisting perception disorder (HPPD) and flashback-are they identical. *Journal of Alcoholism and Drug Dependence, 1*(121), 2.

Horowitz, M. J. (1969). Flashbacks: Recurrent intrusive images after the use of LSD. *The American Journal of Psychiatry, 126*(4), 565–569. https://doi.org/10.1176/ajp.126.4.565

Hughes, M. S., & Lessell, S. (1990). Trazodone-induced palinopsia. *Archives of Ophthalmology, 108*(3), 399–400.

Hysek, C., Simmler, L., Ineichen, M., Grouzmann, E., Hoener, M., Brenneisen, R., Huwyler, J., & Liechti, M. (2011). The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA ("ecstasy") in humans. *Clinical Pharmacology & Therapeutics, 90*(2), 246–255.

Ihde-Scholl, T., & Jefferson, J. W. (2001). Mitrazapine-associated palinopsia. *The Journal of Clinical Psychiatry, 62*(5), 373.

Isbell, H. (1959). Comparison of the reactions induced by psilocybin and LSD-25 in man. *Psychopharmacologia, 1*(1), 29–38. https://doi.org/10.1007/bf00408109

Jay, M. (2019). *Mescaline: A global history of the first psychedelic*. Yale University Press.

Jay, M. (2023). *Psychonauts: Drugs and the making of the modern mind*. Yale University Press.

Johnson, M. W., Richards, W., & Griffiths, R. R. (2008). Human hallucinogen research: Guidelines for safety. *Journal of Psychopharmacology, 22*(6), 603–620. https://doi.org/10.1177/0269881108093587

Johnson, M. W., Andrew Sewell, R., & Griffiths, R. R. (2012). Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. *Drug and Alcohol Dependence, 123*(1–3), 132–140. https://doi.org/10.1016/j.drugalcdep.2011.10.029

Johnson, M. W., Garcia-Romeu, A., Cosimano, M. P., & Griffiths, R. R. (2014). Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology, 28*(11), 983–992. https://doi.org/10.1177/0269881114548296

Johnson, M. W., Griffiths, R. R., Hendricks, P. S., & Henningfield, J. E. (2018). The abuse potential of medical psilocybin according to the 8 factors of the controlled substances act. *Neuropharmacology, 142*, 143–166. https://doi.org/10.1016/j.neuropharm.2018.05.012

Kirkpatrick, M. G., Gunderson, E. W., Perez, A. Y., Haney, M., Foltin, R. W., & Hart, C. L. (2012). A direct comparison of the behavioral and physiological effects of methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology, 219*(1), 109122. https://doi.org/10.1007/s00213-011-2383-4

Kish, S. J., Lerch, J., Furukawa, Y., Tong, J., McCluskey, T., Wilkins, D., Houle, S., Meyer, J., Mundo, E., Wilson, A. A., Rusjan, P. M., Saint-Cyr, J. A., Guttman, M., Collins, D. L., Shapiro, C., Warsh, J. J., & Boileau, I. (2010). Decreased cerebral cortical serotonin transporter binding in ecstasy users: A positron emission tomography/[11C]DASB and structural brain imaging study. *Brain, 133*(6), 17791797. https://doi.org/10.1093/brain/awq103

Klock, J. C., Boerner, U., & Becker, C. E. (1975). Coma, hyperthermia, and bleeding associated with massive LSD overdose a report of eight cases. *Clinical Toxicology, 8*(2), 191–203. https://doi.org/10.3109/15563657508988063

Kometer, M., Schmidt, A., Bachmann, R., Studerus, E., Seifritz, E., & Vollenweider, F. (2012). Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. *Biological Psychiatry, 72*(11), 898–906. https://doi.org/10.1016/j.biopsych.2012.04.005

Koslow, T. (2020). Why taking psychedelics while on antidepressants could make treatment ineffective: DoubleBlind. *Double Blind Magazine*. https://doubleblindmag.com/how-psychedelics-contraindicate-with-ssris/

Kovacic, B., & Domino, E. F. (1976). Tolerance and limited cross-tolerance to the effects of n, n-dimethyltryptamine (DMT) and lysergic acid diethylamide-25 (LSD) on food-rewarded bar pressing in the rat. *Journal of Pharmacology and Experimental Therapeutics, 197*(3), 495–502.

Krebs, T. S., & Johansen, P.-Ø. (2013). Psychedelics and mental health: A population study. *PLoS One, 8*(8), e63972.

Lauterbach, E., Abdelhamid, A., & Annandale, J. (2000). Posthallucinogen-like visual illusions (palinopsia) with risperidone in a patient without previous hallucinogen exposure: Possible relation to serotonin 5HT2a receptor blockade. *Pharmacopsychiatry, 33*(01), 38–41.

Lerner, A. G., Oyffe, I., & Isaacs, G. (1997). Naltrexone treatment of hallucinogen persisting perception disorder. *American Journal of Psychiatry, 154*(3), 437–437.

Lerner, A. G., Gelkopf, M., Oyffe, I., Finkel, B., Katz, S., Sigal, M., & Weizman, A. (2000). LSD-induced hallucinogen persisting perception disorder treatment with clonidine: An open pilot study. *International Clinical Psychopharmacology, 15*(1), 35–37.

Lerner, A. G., Gelkopf, M., Skladman, I., Rudinski, D., Nachshon, H., & Bleich, A. (2003). Clonazepam treatment of lysergic acid diethylamide-induced hallucinogen persisting perception disorder with anxiety features. *International Clinical Psychopharmacology, 18*(2), 101–105.

Lerner, A. G., Goodman, C., Rudinski, D., & Bleich, A. (2011). Benign and time-limited visual disturbances (flashbacks) in recent abstinent high-potency heavy cannabis smokers: A case series study. *The Israel Journal of Psychiatry and Related Sciences, 48*, 25–29.

Lerner, A. G., Rudinski, D., Bor, O., & Goodman, C. (2014). Flashbacks and HPPD: A clinical-oriented

concise review. *Israel Journal of Psychiatry and Related Sciences, 51*(4), 296–302.

Lev-Ran, S., Feingold, D., Frenkel, A., & Lerner, A. G. (2014). Clinical characteristics of individuals with schizophrenia and hallucinogen persisting perception disorder: A preliminary investigation. *Journal of Dual Diagnosis, 10*(2), 79–83.

Lieberman, J. A., Kane, J. M., & Alvir, J. (1987). Provocative tests with psychostimulant drugs in schizophrenia. *Psychopharmacology, 91*(4), 415433. https://doi.org/10.1007/BF00216006

Liechti, M. E. (2014). Effects of MDMA on body temperature in humans. *Temperature, 1*(3), 192–200. https://doi.org/10.4161/23328940.2014.955433

Liechti, M. E., & Vollenweider, F. (2000). The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3, 4-methylenedioxymethamphetamine ("ecstasy") in healthy volunteers. *Journal of Psychopharmacology, 14*(3), 269–274.

Liechti, M. E., Gamma, A., & Vollenweider, F. (2001). Gender differences in the subjective effects of MDMA. *Psychopharmacology, 154*(2), 161–168.

Lim, T., Wasywich, C., & Ruygrok, P. (2012). A fatal case of 'magic mushroom' ingestion in a heart transplant recipient. *Internal Medicine Journal, 11*(42), 1268–1269.

Lima, F. A. S., Tófoli, L. F., Labate, B., & Jungaberle, H. (2011). An epidemiological surveillance system by the UDV: Mental health recommendations concerning the religous use of hoasca. *The Internationalization of Ayahuasca*, December 2017.

Litjens, R. P. W., Brunt, T. M., Alderliefste, G.-J., & Westerink, R. H. S. (2014). Hallucinogen persisting perception disorder and the serotonergic system: A comprehensive review including new MDMA-related clinical cases. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology, 24*, 1309–1323. https://doi.org/10.1016/j.euroneuro.2014.05.008

Lovenberg, T. W., Erlander, M. G., Baron, B. M., Racke, M., Slone, A. L., Siegel, B. W., Craft, C. M., Burns, J. E., Danielson, P. E., & Sutcliffe, J. G. (1993). Molecular cloning and functional expression of 5-HT1E-like rat and human 5-hydroxytryptamine receptor genes. *Proceedings of the National Academy of Sciences, 90*(6), 2184–2188. https://doi.org/10.1073/pnas.90.6.2184

Luke, D. P., & Terhune, D. B. (2013). The induction of synaesthesia with chemical agents: A systematic review. *Frontiers in Psychology*, 4. https://doi.org/10.3389/fpsyg.2013.00753

Lurie, Y., Gopher, A., Lavon, O., Almog, S., Sulimani, L., & Bentur, Y. (2011). Severe paramethoxymethamphetamine (PMMA) and paramethoxyamphetamine (PMA) outbreak in Israel. *Clinical Toxicology, 50*(1), 39–43. https://doi.org/10.3109/15563650.2011.635148

Madsen, M. K., Fisher, P. M., Burmester, D., Dyssegaard, A., Stenbæk, D. S., Kristiansen, S., Johansen, S. S., Lehel, S., Linnet, K., Svarer, C., Erritzoe, D., Ozenne, B., & Knudsen, G. M. (2019). Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology, 44*(7), 1328–1334. https://doi.org/10.1038/s41386-019-0324-9

Majić, T., Schmidt, T. T., & Gallinat, J. (2015). Peak experiences and the afterglow phenomenon: When and how do therapeutic effects of hallucinogens depend on psychedelic experiences? *Journal of Psychopharmacology, 29*(3), 241–253.

Marek, G. J., Wright, R. A., Schoepp, D. D., Monn, J. A., & Aghajanian, G. K. (2000). Physiological antagonism between 5-hydroxytryptamine2A and group II metabotropic glutamate receptors in prefrontal cortex. *Journal of Pharmacology and Experimental Therapeutics, 292*(1), 76–87.

Markel, H., Lee, A., Holmes, R. D., & Domino, E. F. (1994). LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. *The Journal of Pediatrics, 125*(5), 817–819.

Mas, M., Farré, M., de la Torre, R., Roset, P. N., Ortuño, J., Segura, J., & Camí, J. (1999). Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. *Journal of Pharmacology and Experimental Therapeutics, 290*(1), 136–145.

Masters, R. E., & Houston, J. (1966). *The varieties of psychedelic experience* (Vol. 9289). Holt, Rinehart and Winston.

McCann, U. D., Ridenour, A., Shaham, Y., & Ricaurte, G. A. (1994). Serotonin neurotoxicity after (±)3,4-methylenedioxymethamphetamine (MDMA "ecstasy"): A controlled study in humans. *Neuropsychopharmacology, 10*(2), 129138. https://doi.org/10.1038/npp.1994.15

McCann, U. D., Mertl, M., Eligulashvili, V., & Ricaurte, G. A. (1999). Cognitive performance in(–) 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') users: A controlled study. *Psychopharmacology, 143*(4), 417425. https://doi.org/10.1007/s002130050967

McCann, U. D., Szabo, Z., Seckin, E., Rosenblatt, P., Mathews, W. B., Ravert, H. T., Dannals, R. F., & Ricaurte, G. A. (2005). Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB. *Neuropsychopharmacology, 30*(9), 17411750. https://doi.org/10.1038/sj.npp.1300736

McDowell, D. M., & Kleber, H. D. (1994). MDMA: Its history and pharmacology. *Psychiatric Annals, 24*(3), 127130. https://doi.org/10.3928/0048-5713-19940301-06

McGlothlin, W. H., & Arnold, D. O. (1971). LSD revisited: A ten-year follow-up of medical LSD use. *Archives of General Psychiatry, 24*(1), 35–49. https://doi.org/10.1001/archpsyc.1971.01750070037005

McGuire, P., & Fahy, T. (1991). Chronic paranoid psychosis after misuse of MDMA ("ecstasy"). *BMJ: British Medical Journal, 302*(6778), 697.

Mcguire, P. K., Cope, H., & Fahy, T. A. (1994). Diversity of psychopathology associated with use of 3, 4-methylenedioxymethamphetamine ("ecstasy"). *The British Journal of Psychiatry, 165*(3), 391–395.

McKenna, T. (1992). *Food of the gods: A radical history of plants, drugs and human evolution*. Rider.

McKetin, R., Copeland, J., Norberg, M. M., Bruno, R., Hides, L., & Khawar, L. (2014). The effect of the ecstasy 'come-down'on the diagnosis of ecstasy dependence. *Drug and Alcohol Dependence, 139*, 26–32.

Miech, R., Johnston, L., O'Malley, P., Bachman, J., Schulenberg, J., & Patrick, M. (2020). *Monitoring the future national survey results on drug use, 1975–2019: Volume I, secondary school students*. Ann Arbor, MI: Institute for Social Research, University of Michigan.

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., & Doblin, R. (2011). The safety and efficacy of$$3, 4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: The first randomized controlled pilot study. *Journal of Psychopharmacology, 25*(4), 439–452.

Mithoefer, M. C., Mithoefer, A., Feduccia, L., et al. (2018). MDMA-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry, 55*(6), 486–497.

Molliver, M. E., Berger, U. V., Mamounas, L. A., Molliver, D. C., O'Hearn, E., & Wilson, M. A. (1990). *Neurotoxicity of MDMA and related compounds: Anatomic studies* (Vol. 600, pp. 641–661). Annals of the New York Academy of Sciences.

Morehead, D. B. (1997). Exacerbation of hallucinogen-persisting perception disorder with risperidone. *Journal of Clinical Psychopharmacology, 17*(4), 327–328.

Morgan, M. J. (1998). Recreational use of 'ecstasy' (MDMA) is associated with elevated impulsivity. *Neuropsychopharmacology, 19*(4), 252264. https://doi.org/10.1016/S0893-133X(98)00012-8

Moritz, M. L., Kalantar-Zadeh, K., & Ayus, J. C. (2013). Ecstacy-associated hyponatremia: Why are women at risk? *Nephrology Dialysis Transplantation, 28*(9), 2206–2209.

Moskowitz, D. (1971). Use of haloperidol to reduce LSD flashbacks. *Military Medicine, 136*(9), 754–756.

Mueller, M., Kolbrich, E. A., Peters, F. T., Maurer, H. H., McCann, U. D., Huestis, M. A., & Ricaurte, G. A. (2009). Direct comparison of (±) 3,4-methylenedioxymethamphetamine ("ecstasy") disposition and metabolism in squirrel monkeys and humans. *Therapeutic Drug Monitoring, 31*(3), 367–373. https://doi.org/10.1097/ftd.0b013e3181a4f6c2

Mueller, M., Yuan, J., McCann, U. D., Hatzidimitriou, G., & Ricaurte, G. A. (2013). Single oral doses of (±) 3,4-methylenedioxymethamphetamine ('ecstasy') produce lasting serotonergic deficits in non-human primates: Relationship to plasma drug and metabolite concentrations. *International Journal of Neuropsychopharmacology, 16*(4), 791801. https://doi.org/10.1017/S1461145712000582

Mueller, F., Lenz, C., Steiner, M., Dolder, P., Walter, M., Lang, U., Liechti, M., & Borgwardt, S. (2016). Neuroimaging in moderate MDMA use: A systematic review. *Neuroscience & Biobehavioral Reviews, 62*, 21–34.

Murphy, T. P. (1993). Mal de debarquement syndrome: A forgotten entity? *Otolaryngology–Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery, 109*, 10–13. https://doi.org/10.1177/019459989310900103

Naditch, M. P., & Fenwick, S. (1977). LSD flashbacks and ego functioning. *Journal of Abnormal Psychology, 86*(4), 352.

Nichols, D. E. (2004). Hallucinogens. *Pharmacology & Therapeutics, 101*(2), 131–181. https://doi.org/10.1016/j.pharmthera.2003.11.002

O'hearn, E., Battaglia, G., De Souza, E., Kuhar, M., & Molliver, M. (1988). Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of serotonergic axon terminals in forebrain: Immunocytochemical evidence for neurotoxicity. *Journal of Neuroscience, 8*(8), 2788–2803.

Organization, W. H. (2004). *International statistical classification of diseases and related health problems: Instruction manual* (Vol. 2). World Health Organization.

Ortiz Bernal, A. M., Raison, C. L., Lancelotta, R. L., & Davis, A. K. (2022). Reactivations after 5-methoxy-N, N-dimethyltryptamine use in naturalistic settings: An initial exploratory analysis of the phenomenon's predictors and its emotional valence. *Frontiers in Psychiatry, 13*, 1049643.

Palamar, J. J. (2017). What's in a name? Correlates of ecstasy users knowing or agreeing that molly is ecstasy/MDMA. *Journal of Psychoactive Drugs, 50*(1), 88–93. https://doi.org/10.1080/02791072.2017.1369200

Palamar, J. J., Keyes, K., & Cleland, C. M. (2016). Underreporting of ecstasy use among high school seniors in the US. *Drug and Alcohol Dependence, 165*, 279–282. https://doi.org/10.1016/j.drugalcdep.2016.06.001

Palamar, J. J., Acosta, P., Ompad, D. C., & Cleland, C. M. (2017). Self-reported ecstasy/MDMA/"molly" use in a sample of nightclub and dance festival attendees in New York city. *Substance Use & Misuse, 52*(1), 82–91.

Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., Mota-Rolim, S. A., Osório, F. L., Sanches, R., dos Santos, R. G., Tófoli, L. F., de Oliveira Silveira, G., Yonamine, M., Riba, J., Santos, F. R., Silva-Junior, A. A., Alchieri, J. C.,

Galvão-Coelho, N. L., Lobão-Soares, B., et al. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: A randomized placebo-controlled trial. *Psychological Medicine, 49*(4), 655–663. https://doi.org/10.1017/S0033291718001356

Palmieri, V., Arnett, D. K., Roman, M. J., Liu, J. E., Bella, J. N., Oberman, A., Kitzman, D. W., Hopkins, P. N., Morgan, D., de Simone, G., et al. (2002). Appetite suppressants and valvular heart disease in a population-based sample: The HyperGEN study. The American Journal of Medicine, 112(9), 710–715.

Pantoni, M. M., & Anagnostaras, S. G. (2019). Cognitive effects of MDMA in laboratory animals: A systematic review focusing on dose. *Pharmacological Reviews, 71*(3), 413–449. https://doi.org/10.1124/pr.118.017087

Parrott, A. C. (2004). Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. *Psychopharmacology, 173*(3–4), 234–241. https://doi.org/10.1007/s00213-003-1712-7

Parrott, A. C., & Young, L. (2014). Saturday night fever in ecstasy/MDMA dance clubbers: Heightened body temperature and associated psychobiological changes. *Temperature, 1*(3), 214–219. https://doi.org/10.4161/23328940.2014.977182

Parrott, A. C., Rodgers, J., Buchanan, T., Ling, J., Heffernan, T., & Scholey, A. B. (2006). Dancing hot on ecstasy: Physical activity and thermal comfort ratings are associated with the memory and other psychobiological problems reported by recreational MDMA users. *Human Psychopharmacology: Clinical and Experimental, 21*(5), 285–298.

Passie, T. (2018). The early use of MDMA ('ecstasy') in psychotherapy (19771985). *Drug Science, Policy and Law, 4*, 205032451876744. https://doi.org/10.1177/2050324518767442

Passie, T., Halpern, J., Stichtenoth, D. O., Emrich, H. M., & Hintzen, A. (2008). The pharmacology of lysergic acid diethylamide: A review. *CNS Neuroscience & Therapeutics, 14*(4), 295314. https://doi.org/10.1111/j.1755-5949.2008.00059.x

Patel, A., Moreland, T., Haq, F., Siddiqui, F., Mikul, M., Qadir, H., & Raza, S. (2011). Persistent psychosis after a single ingestion of "ecstasy" (MDMA). *The Primary Care Companion to CNS Disorders, 13*(6).

Peiró, A. M., Farré, M., Roset, P. N., Carbó, M., Pujadas, M., Torrens, M., Camí, J., & De La Torre, R. (2013). Human pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) after repeated doses taken 2 h apart. *Psychopharmacology, 225*(4), 883893. https://doi.org/10.1007/s00213-012-2894-7

Pellikka, P. A., Tajik, A. J., Khandheria, B. K., Seward, J. B., Callahan, J. A., Pitot, H. C., & Kvols, L. K. (1993). Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation, 87*(4), 1188–1196.

Pentney, A. R. (2001). An exploration of the history and controversies surrounding MDMA and MDA. *Journal of Psychoactive Drugs, 33*(3), 213221. https://doi.org/10.1080/02791072.2001.10400568

Peroutka, S. J., Newman, H., & Harris, H. (1988). Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology, 1*(4), 273277. https://www.researchgate.net/publication/20248279

Potash, M. N., Gordon, K. A., & Conrad, K. L. (2009). Persistent psychosis and medical complications after a single ingestion of MDMA "ecstasy": A case report and review of the literature. *Psychiatry (Edgmont), 6*(7), 40.

Preller, K., Herdener, M., Pokorny, T., Planzer, A., Kraehenmann, R., Stämpfli, P., Liechti, M. E., Seifritz, E., & Vollenweider, F. (2017). The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation. *Current Biology, 27*(3), 451–457. https://doi.org/10.1016/j.cub.2016.12.030

Reneman, L., Booij, J., Schmand, B., Van Den Brink, W., & Gunning, B. (2000). Memory disturbances in 'ecstasy' users are correlated with an altered brain serotonin neurotransmission. *Psychopharmacology, 148*(3), 322324. https://doi.org/10.1007/s002130050057

Renfroe, C. L. (1986). MDMA on the street: Analysis anonymous. *Journal of Psychoactive Drugs, 18*(4), 363–369. https://doi.org/10.1080/02791072.1986.10472371

Reynolds, H. T., Vijayakumar, V., Gluck-Thaler, E., Korotkin, H. B., Matheny, P. B., & Slot, J. C. (2018). Horizontal gene cluster transfer increased hallucinogenic mushroom diversity. *Evolution Letters, 2*(2), 88–101.

Ricaurte, G. A., Yuan, J., Hatzidimitriou, G., Cord, B. J., & McCann, U. D. (2002). Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy"). *Science, 297*(5590), 2260–2263.

Rogers, G., Elston, J., Garside, R., Roome, C., Taylor, R., Younger, P., Zawada, A., & Somerville, M. (2009). The harmful health effects of recreational ecstasy: A systematic review of observational evidence. *Health Technology Assessment, 13*(6). https://doi.org/10.3310/hta13060

Roiser, J. P., & Sahakian, B. J. (2004). Relationship between ecstasy use and depression: A study controlling for poly-drug use. *Psychopharmacology, 173*(3–4), 411417. https://doi.org/10.1007/s00213-003-1705-6

Rosenberg, D. E., Isbell, H., Miner, E. J., & Logan, C. R. (1964). The effect of n,n-dimethyltryptamine in human subjects tolerant to lysergic acid diethylamide. *Psychopharmacologia, 5*(3), 217–227. https://doi.org/10.1007/BF00413244

Rosenthal, S. H. (1964). Persistent hallucinosis following repeated administration of hallucinogenic drugs. *American Journal of Psychiatry, 121*(3), 238–244.

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K.,

Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology, 30*(12), 1165–1180. https://doi.org/10.1177/0269881116675512

Rothman, R. B., Baumann, M. H., Savage, J. E., Rauser, L., McBride, A., Hufeisen, S. J., & Roth, B. L. (2000). Evidence for possible involvement of 5-HT2B receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation, 102*(23), 2836–2841.

Sacks, O. (1992). *Migraine*. Vintage Books.

Saleemi, S., Pennybaker, S. J., Wooldridge, M., & Johnson, M. W. (2017). Who is 'molly'? MDMA adulterants by product name and the impact of harm-reduction services at raves. *Journal of Psychopharmacology, 31*(8), 10561060. https://doi.org/10.1177/0269881117715596

Sandison, R. A., & Whitelaw, J. D. (1957). Further studies in the therapeutic value of lysergic acid diethylamide in mental illness. *The Journal of Mental Science, 103*(431), 332–343. https://doi.org/10.1192/bjp.103.431.332

Savage, C., & McCabe, O. L. (1973). Residential psychedelic (LSD) for the narcotic addict. *Archives of General Psychiatry, 28*, 808–814.

Schankin, C., Maniyar, F., Hoffmann, J., Chou, D., & Goadsby, P. (2013). Clinical characterization of "visual snow" (positive persistent visual disturbance). *The Journal of Headache and Pain, 14*(1), 1–1.

Schenk, S. (2009). *MDMA self-administration in laboratory animals: A summary of the literature and proposal for future research., 60*(3–4), 130136. https://doi.org/10.1159/000253549

Schilt, T., de Win, M. M. L., Koeter, M., Jager, G., Korf, D. J., Van Den Brink, W., & Schmand, B. (2007). Cognition in novice ecstasy users with minimal exposure to other drugs: A prospective cohort study. *Archives of General Psychiatry, 64*(6), 728736. https://doi.org/10.1001/archpsyc.64.6.728

Schmid, Y., Rickli, A., Schaffner, A., Duthaler, U., Grouzmann, E., Hysek, C. M., & Liechti, M. E. (2015). Interactions between bupropion and 3, 4-methylenedioxymethamphetamine in healthy subjects. *Journal of Pharmacology and Experimental Therapeutics, 353*(1), 102–111.

Schmidt, C. J. (1987). Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *Journal of Pharmacology and Experimental Therapeutics, 240*(1), 1–7.

Scholey, A. B., Parrott, A. C., Buchanan, T., Heffernan, T. M., Ling, J., & Rodgers, J. (2004). Increased intensity of ecstasy and polydrug usage in the more experienced recreational ecstasy/MDMA users: A WWW study. *Addictive Behaviors, 29*(4), 743–752.

Schulenberg, J., Johnston, L., O'Malley, P., Bachman, J., Miech, R., & Patrick, M. (2020). *Monitoring the future national survey results on drug use, 1975–2019: Volume II, college students and adults ages 19–60*. Ann Arbor, MI: Institute for Social Research, University of Michigan.

Shankaran, M., Yamamoto, B. K., & Gudelsky, G. A. (1999). Involvement of the serotonin transporter in the formation of hydroxyl radicals induced by 3, 4-methylenedioxymethamphetamine. *European Journal of Pharmacology, 385*(2–3), 103–110.

Shick, J. F. E., & Smith, D. E. (1970). Analysis of the LSD flashback. *Journal of Psychedelic Drugs, 3*(1), 13–19.

Shulgin, A., & Shulgin, A. (1991). PIKHAL: A chemical love story. *Transformation, 1*.

Siegel, R. K. (1986). MDMA: Nonmedical use and intoxication. *Journal of Psychoactive Drugs, 18*(4), 349–354. https://doi.org/10.1080/02791072.1986.10472368

Smart, R., & Bateman, K. (1967). Unfavourable reactions of LSD: A review and analysis of the available case reports. *Canadian Medical Association Journal, 97*, 1214–1221.

Smirnov, A., Najman, J. M., Hayatbakhsh, R., Plotnikova, M., Wells, H., Legosz, M., & Kemp, R. (2013). Young adults' trajectories of ecstasy use: A population based study. *Addictive Behaviors, 38*(11), 2667–2674.

Stace, W. T. (1960). *The teachings of the mystics: Being selections from the great mystics and mystical writings of the world*. New American Library.

Stanton, M. D., & Bardoni, A. (1972). Drug flashbacks: Reported frequency in a military population. *American Journal of Psychiatry, 129*(6), 751–755.

Strassman, R. J. (1984). Adverse reactions to psychedelic drugs. *The Journal of Nervous and Mental Disease, 172*(10), 577–595. https://doi.org/10.1097/00005053-192210000-00085

Strassman, R. J., Qualls, C. R., & Berg, L. M. (1996). Differential tolerance to biological and subjective effects of four closely spaced doses of n, n-dimethyltryptamine in humans. *Biological Psychiatry, 39*(9), 784–795. https://doi.org/10.1016/0006-3223(95)00200-6

Studerus, E., Kometer, M., Hasler, F., & Vollenweider, F. (2011). Acute, subacute and long-term subjective effects of psilocybin in healthy humans: A pooled analysis of experimental studies. *Journal of Psychopharmacology, 25*(11), 1434–1452.

Subramanian, N., & Doran, M. (2014). Improvement of hallucinogen persisting perception disorder (HPPD) with oral risperidone: Case report. *Irish Journal of Psychological Medicine, 31*(1), 47–49.

Szmulewicz, A. G., Valerio, M. P., & Smith, J. M. (2015). Switch to mania after ayahuasca consumption in a man with bipolar disorder: A case report. *International Journal of Bipolar Disorders, 3*(1), 1–3.

Thomasius, R., Petersen, K., Buchert, R., Andresen, B., Zapletalova, P., Wartberg, L., Nebeling, B., & Schmoldt, A. (2003). Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. *Psychopharmacology, 167*(1), 8596. https://doi.org/10.1007/s00213-002-1383-9

Thomasius, R., Zapletalova, P., Petersen, K., Buchert, R., Andresen, B., Wartberg, L., Nebeling, B., & Schmoldt, A. (2006). Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: The longitudinal perspective. *Journal of Psychopharmacology, 20*(2), 211225. https://doi.org/10.1177/0269881106059486

Togni, L. R., Lanaro, R., Resende, R. R., & Costa, J. L. (2015). The variability of ecstasy tablets composition in Brazil. *Journal of Forensic Sciences, 60*(1), 147–151.

Ungerleider, J. T., & Frank, I. (1976). Management of acute panic reactions and drug flashbacks resulting from LSD ingestion. *Acute Drug Emergencies*, 133–138.

Ungerleider, J. T., Fisher, D. D., & Fuller, M. (1966). The dangers of LSD: Analysis of seven months' experience in a university hospital's psychiatric service. *JAMA, 197*(6), 389–392.

Ungerleider, J. T., Fisher, D. D., Goldsmith, S. R., Fuller, M., & Forgy, E. (1968). A statistical survey of adverse reactions to LSD in Los Angeles county. *American Journal of Psychiatry, 125*(3), 352–357.

Uosukainen, H., Tacke, U., & Winstock, A. R. (2015). Self-reported prevalence of dependence of MDMA compared to cocaine, mephedrone and ketamine among a sample of recreational poly-drug users. *International Journal of Drug Policy, 26*(1), 78–83.

Urban, N. B. L., Girgis, R. R., Talbot, P. S., Kegeles, L. S., Xu, X., Frankle, W. G., Hart, C. L., Slifstein, M., Abi-Dargham, A., & Laruelle, M. (2012). Sustained recreational use of ecstasy is associated with altered pre and postsynaptic markers of serotonin transmission in neocortical areas: A PET study with 11 CDASB and 11 CMDL 100907. *Neuropsychopharmacology, 37*(6), 14651473. https://doi.org/10.1038/npp.2011.332

Vaiva, G., Boss, V., Bailly, D., Thomas, P., Lestavel, P., & Goudemand, M. (2001). An "accidental" acute psychosis with ecstasy use. *Journal of Psychoactive Drugs, 33*(1), 9598. https://doi.org/10.1080/02791072.2001.10400473

Valle, M., Maqueda, A. E., Rabella, M., Rodríguez-Pujadas, A., Antonijoan, R. M., Romero, S., Alonso, J. F., Mañanas, M. À., Barker, S., Friedlander, P., et al. (2016). Inhibition of alpha oscillations through serotonin-2A receptor activation underlies the visual effects of ayahuasca in humans. *European Neuropsychopharmacology, 26*(7), 1161–1175.

Verbaten, M. N. (2003). Specific memory deficits in ecstasy users? The results of a meta-analysis. *Human Psychopharmacology: Clinical and Experimental, 18*(4), 281–290. https://doi.org/10.1002/hup.482

Verheyden, S. L., Hadfield, J., Calin, T., & Curran, V. H. (2002). Sub-acute effects of MDMA (3,4-methylenedioxymethamphetamine, "ecstasy") on mood: Evidence of gender differences. *Psychopharmacology, 161*(1), 2331. https://doi.org/10.1007/s00213-001-0995-9

Verheyden, S. L., Henry, J. A., & Curran, H. V. (2003). Acute, sub-acute and long-term subjective consequences of "ecstasy" (MDMA) consumption in 430 regular users. *Human Psychopharmacology: Clinical and Experimental, 18*(7), 507–517. https://doi.org/10.1002/hup.529

Vollenweider, F. (1999). 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in mana PET study with [11C]raclopride. *Neuropsychopharmacology, 20*(5), 424–433. https://doi.org/10.1016/s0893-133x(98)00108-0

Vollenweider, F., & Preller, K. (2020). Psychedelic drugs: Neurobiology and potential for treatment of psychiatric disorders. *Nature Reviews Neuroscience, 21*(11), 611–624. https://doi.org/10.1038/s41583-020-0367-2

Vollenweider, F., Vollenweider-Scherpenhuyzen, M. F., Bäbler, A., Vogel, H., & Hell, D. (1998). Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport, 9*(17), 3897–3902.

Von Sydow, K., Lieb, R., Pfister, H., Höfler, M., & Wittchen, H. U. (2002). Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults – a transient phenomenon? Results from a longitudinal community study. *Drug and Alcohol Dependence, 66*(2), 147159. https://doi.org/10.1016/S0376-8716(01)00195-8

Vuori, E., Henry, J. A., Ojanperä, I., Nieminen, R., Savolainen, T., Wahlsten, P., & Jäntti, M. (2003). Death following ingestion of MDMA (ecstasy) and moclobemide. *Addiction, 98*(3), 365–368.

Wallace, A. F. (1959). Cultural determinants of response to hallucinatory experience. *AMA Archives of General Psychiatry, 1*(1), 58–69. https://doi.org/10.1001/archpsyc.1959.03590010074009

Waters, F., Collerton, D., Ffytche, D. H., Jardri, R., Pins, D., Dudley, R., Blom, J. D., Mosimann, U. P., Eperjesi, F., Ford, S., & Larøi, F. (2014). Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease. *Schizophrenia Bulletin, 40*(Suppl_4), S233–S245. https://doi.org/10.1093/schbul/sbu036

Williams, H., Meagher, D., & Galligan, P. (1993). MDMA ("ecstasy"); a case of possible drug-induced psychosis. *Irish Journal of Medical Science, 162*(2), 43.

Wolbach, A. B., Isbell, H., & Miner, E. (1962). Cross tolerance between mescaline and LSD-25 with a comparison of the mescaline and LSD reactions. *Psychopharmacologia, 3*(1), 1–14.

Wu, L.-T., Ringwalt, C. L., Mannelli, P., & Patkar, A. A. (2008). Hallucinogen use disorders among adult users of MDMA and other hallucinogens. *American Journal on Addictions, 17*(5), 354–363. https://doi.org/10.1080/10550490802269064

Wunderli, M. D., Vonmoos, M., Fürst, M., Schädelin, K., Kraemer, T., Baumgartner, M. R., Seifritz, E., & Quednow, B. B. (2017). Discrete memory impairments in largely pure chronic users of MDMA. *European Neuropsychopharmacology, 27*(10), 987999. https://doi.org/10.1016/j.euroneuro.2017.08.425

Young, C. R. (1997). Sertraline treatment of hallucinogen persisting perception disorder. *The Journal of Clinical Psychiatry, 58*(2), 85.