The 21st Century Revival of Therapeutic Research on Classic Psychedelic Drugs: Antecedents, Evidence and Potential Future Medical and other Uses

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Contents

1 Executive Summary

Clinical research on psychedelic drugs in psychiatry that was abandoned at the end of the 1970s has undergone a revival over the past two decades. This paper describes the Western discovery of the psychedelic drugs; clinical research on their therapeutic uses in the 1950s and 1960s; the reasons for its abandonment in the 1970s and its revival in the 1990s; and the results of recent clinical research on therapeutic uses of psychedelic drugs.

Terminology

A psychedelic drug is one which "produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis" in the absence of "physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia". The "classic psychedelic drugs" mescaline, psilocybin, and LSD share the property of stimulating the 5HT-2a serotonin receptor.

Evolutionary origins of psychedelic drugs

Substances found in mushrooms, cacti and plant seeds produce psychedelic effects in humans because evolution selected plants that produced chemicals that attracted insects to pollinate them and deterred insects and snails and slugs from eating them. These chemicals affect human central nervous systems which are biochemically, architecturally and functionally very similar to those of insects.

The Western discovery of psychedelic drugs

The psychedelic effects of mushrooms, cacti, and seeds were discovered by the indigenous peoples of Central and South America who used them for religious and healing purposes for centuries. Mescaline was the first psychedelic extracted from the peyote cactus in 1897 and synthesised in 1919.The Swiss chemist, Albert Hofmann's discovered the psychedelic effects of LSD and isolated psilocybin in mushrooms and a hallucinogen in the seeds of a Mexican plant which proved to be a naturally occurring derivative of lysergic acid.

Mescaline and LSD as "model psychoses"

In the 1930s and 1940s, psychiatrists argued that because mescaline produced some symptoms of schizophrenia that these psychoses were caused by a "toxic amine". Stronger support emerged for the hypothesis that psychotic symptoms were caused by disturbed dopamine function.

LSD treatment of alcoholism

In the late 1950s, Osmond and Hoffer used LSD to treat alcohol dependence. They thought that LSD would produce psychotic symptoms that would 'scared' alcoholics into sobriety but found that it more often produced a mystical epiphany that led their patients to cease drinking. They reported that 50% of the patients were abstinent 6 to 12 months after treatment. Sceptical colleagues argued that their studies were poorly controlled, involved only small numbers of patients and that assessments of treatment outcomes were biased.

Randomised controlled trials of patients given LSD found no differences in outcome after 12-18 months.

Psychotherapy for anxiety and depressive disorders

Psychiatrists that the use of low doses of LSD to assist in psychodynamic psychotherapy for anxiety and depressive disorders produced improvements in 70% of their patients. Some clinicians also reported that LSD substantially reduced their anxiety and depression in terminally ill cancer patients.

Psychedelic drugs and mystical experiences

Aldous Huxley popularised the idea that psychedelic drugs could be used for spiritual enlightenment. He argued that mescaline bypassed the "cerebral reducing valve" that enabled human beings to function in everyday life. Timothy Leary gave psilocybin and LSD to Harvard students and prisoners in the 1960s. After leaving Harvard in 1963 he advocated LSD use as a religious sacrament and encouraged young people to "tune in, turn on and drop out". LSD became a rite of passage in the "counterculture" of the late 1960s. Richard Nixon responded to public alarm by banning LSD use under US Federal law in 1970.

Morally questionable uses of psychedelic drugs

In the 1950s the US Army, funded research on using LSD to disable enemy troops and the CIA conducted research on the use of LSD to interrogate foreign spies. The CIA also gave LSD to its employees and civilians without their knowledge or consent.

Charles Manson used LSD to recruit young women into his "Family" whom he convinced to commit murders in Los Angeles in 1969. His 1970 trial generated enormous adverse publicity for LSD. In Australia, Anne Hamilton-Burns, used LSD to create an Australian "Family" in the 1970s whose members believed she was a reincarnation of Jesus Christ**.**

Why was research on the psychedelics abandoned in the USA in the 1970s?

Historical scholarship provides a more complex explanation of how, why and when research on psychedelic drugs ended than the passage of the Controlled Substances Act in 1970.

New pharmaceutical regulations

In 1962 new US legislation tightened the regulation of research on all new drugs by requiring a formal Clinical Trial Notification (CTN) that included preclinical evidence that the drug was safe and likely to be effective and a protocol for a randomised controlled trial.

Calls for tighter regulation of medical use of LSD

Leading medical practitioners called for tighter controls on clinical uses of LSD because some patients reportedly developed psychoses and made suicide attempts. Leary's advocacy of nonmedical psychedelic use also led Sandoz to decide not to longer provide LSD to clinicians and only supply LSD to researchers working in universities and hospitals. Clinical research on psychedelic drugs continued until 1979 but the results were less positive than

those of early researchers and researchers became concerned that their reputations would be damaged by doing such research.

The revival of research on psychedelic drugs in the 1990s

In the 1990s neuroscientists explored the mechanisms of actions of psychedelic drugs in animals and humans and in 2006 the first clinical study of psilocybin in humans was published. A major driver of this revival was the determination of some researchers to explore the role of psychedelic drugs in treating depression and anxiety. Another was the publication of sympathetic histories and positive assessments of early psychedelic research.

Continuities between early and recent psychedelic research

Contemporary research has also focused on the therapeutic use of psychedelics in alcohol and drug dependence, depression and anxiety, and distress in patients with terminal cancer. Early trials were funded from philanthropic sources but for-profit companies have funded recent trials of MDMA and psilocybin.

21st century psychedelic research is done in major research universities in the USA, the UK and Europe whereas early work was done by clinicians in mental hospitals. Current investigators are experienced in conducting controlled clinical trials to the standard required for approval by the FDA.

These researchers have studied psilocybin because it has a shorter period of action (4-6 hours) than LSD (8-12 hours), its pharmacology is better understood, and it does not carry the countercultural baggage of LSD. They have also advised against nonmedical use of psychedelics.

How safe are psychedelic drugs?

Acute adverse effects

No fatal overdoses have been reported from using psychedelic drugs. The estimated human lethal dose of LSD is much greater than typical psychedelic doses.

Adverse events are rare among patients given LSD under medical supervision. “Bad trips” were more common among nonmedical users in the 1960s. Psychoses and suicides have been rare and it is difficult to decide what role LSD played in these deaths. Accidental deaths can occur if individuals jump or fall from buildings after taking LSD. The most common short-term adverse effect of psilocybin in laboratory studies is anxiety (around a third). Most other adverse effects were minor: fatigue, headaches, lack of energy, and difficulty concentrating after taking the drug.

Long term adverse effects

There are limited data on the long-term adverse effects of psychedelic drugs. The “acute anxiety or fear” reported by around a third of persons given psilocybin do not persist. Nor do the “flashbacks” that can be reported in the days after a psychedelic experience.

Abuse and dependence potential of psychedelics

Psilocybin has a very low abuse potential because it does not produce euphoria, animals will not self-administer, and problems related to psychedelic use are rare among persons seeking medical help or treatment for problem drug use. The same appears true of most classic psychedelics.

The risks of heightened suggestibility under psychedelic drugs

Heightened suggestibility is a common effect of psychedelic drugs that can be used for malign purposes by unscrupulous persons. Persons administering these drugs clinically can develop grandiose beliefs about their therapeutic abilities.

Evaluating the effectiveness of psychedelics for medical use

Patients generally know if they have received a psychedelic drug in clinical trials. Researchers have addressed this challenge by using an "active placebo", or low, moderate and high doses of the psychedelic drug to see if treatment effects are dose-related. These approaches have been criticised but the FDA will accept evidence from these trials for regulatory approval.

How effective is psilocybin in treating anxiety and depression?

Meta-analyses of a small numbers of small sample studies have reported greater reductions in depression and anxiety in patients given psilocybin than patients in the control condition. Many of these were cross-over trials which makes blinding impossible. A recent larger trial of psilocybin compared to a SSRI antidepressant provided similar results.

MDMA and Post Traumatic Stress Disorder

A meta-analysis of a series of small phase 2 trials of MDMA-assisted psychotherapy in PTSD found greater reductions in the severity of PTSD symptoms in patients given a high dose of MDMA than those in the low dose or psychotherapy only groups. MDMA-AP appears to produce symptom reductions similar to those of exposure-based psychotherapies and larger reductions than antidepressants approved to treat PTSD. These studies had a median of 18 patients and excluded anyone with comorbid major depression and substance use disorders. The trials were also conducted by MAPS, an organisation that has advocated for psychedelic treatment of PTSD.

Limitations of psychedelic drugs trials

The trials of psychedelic drugs share limitations of early trials of all new drug treatments. They involve small samples of highly selected patients and their results are often much better than results in unselected patient samples in routine clinical practice. The hope and hype that accompany the introduction of "promising" new treatments may amplify placebo responses.

The mechanisms of action of psychedelic-assisted psychotherapies

Psilocybin disrupts the resting "default mode network" (DMN) of the brain, increasing connectivity between brain regions, "open-mindedness" and well-being. Psychedelic drugs

also have anti-inflammatory effects and promote dendrite growth in the hippocampus and amygdala.

It is unclear whether mystical experiences are necessary for effective psychedelic treatment. The role of psychotherapy is also unclear. We also do not know whether intensive MDMA assisted treatment for PTSD is essential or shorter forms of psychotherapy may be just as effective.

How likely are psychedelics to enter medical use?

If the early positive findings are replicated in larger trials psilocybin may be approved to treat depression that does not respond to SSRIs. There is likely to be demand for its use in all forms of depression because one or two treatments that produce immediate improvement would be more attractive than taking antidepressant drugs long term. Psilocybin may also be used off label to treat common anxiety disorders.

If MDMA-assisted psychotherapy is approved to treat PTSD, the cost of its associated psychotherapy may limit access. This may stimulate research into using shorter forms of psychotherapy.

Compassionate access to psychedelics

Advocacy groups argue that patients should have early access to psychedelic drugs before regulatory approval because there is an urgent need for more effective treatments of depression and PTSD. The risks of allowing early access include use of psychedelics to treat conditions in which there is limited evidence and reducing the incentives for conducting clinical trials of these drugs.

Legalisation of psychedelic drugs for religious uses

Some advocates of psychedelic drugs see the legalisation of their medical use as facilitating the legalisation of adult use. Others advocate for the legalisation of psychedelic drugs arguing it should be regarded as a form of religious practice.

Legalisation of adult psychedelic use

Libertarians argue that the state should not interfere in the right of adults to engage in behaviour that may harm themselves, provided that this does not harm others. Citizen initiated referenda are underway in the USA to legalise the use of plant-based psychedelic drugs.

Conclusions

Psychedelic assisted psychotherapy using psilocybin and MDMA has shown promise in treating depression, post-traumatic stress disorders and addiction in small sample studies. There is pressure for early access to psychedelic therapies before larger trials have been completed. The history of psychedelic therapies provides strong grounds for caution in how psychedelic therapies are introduced into routine clinical practice.

2 Glossary

AA	Alcoholics Anonymous
AIDS	Acquired Immunodeficiency Syndrome
ACT-UP	AIDS Coalition to Unleash Power
APA	American Psychiatric Association (USA)
CIA	Central Intelligence Agency (USA)
CSA	Controlled Substances Act (USA)
DMT	Dimethyltryptamine
DSM-5	Diagnostic and Statistical Manual of the APA 5th edition
DMN	Default mode network
DTs	Delirium tremens
FDA	Food and Drug Administration (USA)
HPPD	Hallucinogen persistent perceptual disorder
ICD-10	The International Classification of Diseases 10th edition
LSD	Lysergic acid diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MDD	Major depressive disorder
MDMA	3,4-Methylenedioxymethamphetamine
NIDA	National Institute on Drug Abuse (USA)
NIMH	National Institute for Mental Health (USA)
PTSD	Post Traumatic Stress Disorder
SSRI	Selective serotonin re-uptake inhibitor
WHO	World Health Organization

3 Introduction

Clinical research on classic psychedelic drugs in psychiatry has undergone a revival over the past decade and a half with the conduct of an increasing number of clinical trials of psilocybin and other psychedelic drugs in treating depression, anxiety and addictions [1,2]. Research on the use of LSD to treat addiction in the 1950s and anxiety and depression in the 1960s has been sympathetically re-examined [3,4] in the light of recent historical accounts [5,6,7,8] and the reasons for the abandonment of psychedelic research in the 1970s have been re-examined as well [9,10,11,12]. The revival of interest in psychedelics has been popularised by a best-selling book [3] and by social histories of psychedelic drug use in the USA [13,14,15,16].

This paper briefly describes the European discovery of the psychedelic effects of plant-based drugs from the Americas, the synthesis of LSD and psilocybin in the 1940s and 1950s, clinical research on the therapeutic uses of LSD in the 1950s and 1960s, and the reasons for the abandonment of psychedelic research in North America in the 1970s [17]. It then discusses the factors that have contributed to renewed research interest in psychedelic drugs; describes how recent psychedelic research is related to the earlier research; and summarises the type of research that has been done and what it has shown. It briefly discusses how the clinical use of psychedelic drugs may be regulated to treat addiction and mental disorders. It also considers the arguments for governments allowing the nonmedical use of psychedelic drugs by adults.

3.1 Terminology

Various terms have been used to describe psychedelic drugs [3]. The older term "hallucinogenic" is still used by the US National Library of Medicine to describe their capacity to produce what are described as hallucinations [18]. The related term "psychotomimetic", refers to the putative capacity of these drugs to mimic the symptoms of psychoses by producing hallucinations, delusions and depersonalisation [3]. "Psycholytic" was the term used by psychodynamic psychotherapists in the 1950s to refer to the "mind-loosening" effects of psychedelic drugs that they believed provided access to the unconscious causes of patients' mental disorders [3]. Advocates of the use of psychedelic drugs for spiritual exploration prefer the term "entheogen" [19] which means "manifesting the god within". The most popular term has been "psychedelic", a word coined by Humphry Osmond to mean "mind manifesting" [20,21]. It is the term most often used in the contemporary literature and it is the one that will be used hereafter.

3.2 What are psychedelic drugs?

Grinspoon and Bakalar [22, p. 9] defined a psychedelic drug as one that "produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis" and these

effects occur in the absence of “physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia”.

The boundaries of the category of psychedelic drugs are not well defined [23]. The “classic psychedelic drugs” include mescaline, psilocybin, LSD and DMT (see table 1). Plant-based drugs such as ayahuasca [24] and ibogaine are described as atypical psychedelics [23]. The drug MDMA is nowadays included within the psychedelic category although it does not produce the same perceptual effects of the classic psychedelics [25]. Other drugs, such as, ketamine and PCP [26] have been also described as atypical psychedelics but this discussion will be limited to the classic psychedelics and MDMA.

The classic psychedelics vary in their chemical structures. They include ergolines, phenethylamines and tryptamines. LSD is an ergoline, mescaline is a phenethylamine and psilocybin is a tryptamine. They seem to share the property of stimulating the serotonin receptor system and specifically activating the 5HT-2A receptor [27]. They also act variously on other receptors within the serotonin system and on a variety of other neurotransmitter systems, such as, dopamine and glutamine [23].

Table 1: Psychedelic drugs

Drug	Source	Drug class	Mechanism of action
Mescaline	*Cactaceas* cactus family, including peyote	Phenylethylamine	High affinity 5-HT_{2A} agonist, and even greater affinity to 5-HT_{2C} receptor subtype
5-MeO-DMT	Venom of *Incilius alvarius* (or *Bufo bufo*) toads	Tryptamine	5-HT_2 and 5-HT_{1A} serotonin receptor agonists
d-lysergic acid diethylamide (LSD)	Hydrolysis of ergot fungus derivative	Ergoline	Strong affinity for 5-HT_{2A} and 5-HT_{2C} subtypes
Psilocybin	Various fungi species, most potent *Psilocybe*	Tryptamine	Serotonin 5-HT_{2A} and 5-HT_{2C} agonists
Ibogaine	*Apocynaceae* plant family, including *Tabernantha iboga*	Indole alkaloid	Potent serotonin reuptake inhibitor. Low affinity for 5-HT_{2A} relative to other psychedelics.
Ayahuasca	*Banisteriopsis caapi* vine	Tryptamine (*N*,*N*-DMT) and β-carboline derived alkaloids	MAO inhibition. Modest serotonin 5-HT_{2A} and 5-HT_{2C} agonism

4 The history of psychedelic drugs

4.1 The evolutionary origins of psychedelic drugs

Kennedy [28] suggests that the reason why substances found in mushrooms, cacti and plants produce psychedelic effects in humans lies in the evolutionary histories of plants, insects and humans. All these classes evolved by descent from a single celled common ancestor and share genes that control chemical processes and pathways, including in the case of insects and humans, common brain neurotransmitters [28, p. 44].

Plants, the most abundant living things on earth, evolved first from single celled organisms. They were followed by insects who co-existed with plants for over 400 million years [29,30,31]. During this long period plants and insects co-evolved and evolution selected plants that produced substances that attracted insects to pollinate them and deterred insects and invertebrates, such as snails and slugs, from eating them. It is unlikely that psychedelics evolved to deter herbivorous mammals from eating plants because of the much shorter period that mammals have been on earth [32]. It is much more likely that the intended targets for psychedelic substances found in plants were the insects and invertebrates with which plants and fungi co-evolved [28].

Modern humans emerged several hundred thousand years ago [32], making it even less likely that these substances were selected to act on human brains. It is more plausible that most plant-based drugs affect human brain function because the human central nervous system is "biochemically, architecturally and functionally very similar to that of insects" and can be thought of as "an elaborated version of the insect nervous system" [28, p. 61]. The classic psychedelics primarily act on serotonin (5-HT-2) receptors and these are richly expressed in the areas of the insect brain that control circadian processes, regulate sleep, and promote learning [28]. One of the few animals that produces psychedelic substances (the buffo toad) derives these substances from its insect prey which have symbiotic relationships with the plants that produce psychedelic substances [28].

4.2 A brief history of the Western discovery of psychedelic drugs

The psychedelic effects of mushrooms, cacti, and seeds were discovered by the indigenous peoples of Central and South America who used them for religious and healing purposes for centuries before European colonisation [18,21,28,33]. The first Western descriptions of plant-based psychedelic drugs date from after the 16th century Spanish conquest of the Americas [33,34]. The Spanish made global commodities of the New World "food-drugs" nicotine and chocolate [35,36,37,38] but they discouraged the use of psychedelic plants whose visionary effects they regarded as "satanic" [33,39,40,41]. Indigenous people who used these drugs hid their use from Westerners until the mid-20th century [33,42].

Mescaline was the first plant-based psychedelic substance identified by Europeans. Heffter extracted mescaline from the peyote cactus in 1897 [33] and Spath synthesised it in 1919 [33]. Havelock Ellis, Emile Kraepelin, and Weir Mitchell published reports of their

experiences with the peyote plant in the medical literature [33]. Ellis' account [43] encouraged Aleister Crowley, William Butler Yeats, Jean-Paul Sartre, Walter Benjamin and Anton Artaud to experiment with mescaline [33].

Albert Hofmann's LSD-fuelled bicycle ride in Basel in 1943 is a seminal event in the history of psychedelic drugs [3,18,44]. Hofmann was employed as a chemist at Sandoz, a pharmaceutical company, when in 1938 he synthesised LSD as the 25th derivative of ergotamine, an extract from the ergot fungus. In 1943, Hofmann had an unplanned 'trip' while bicycling home after absorbing LSD through his skin while synthesising the drug [45]. Hofmann described the effects as "a not unpleasant intoxicated-like state characterized by an extremely stimulated imagination … [and] an interrupted stream of fantastic pictures, extraordinary shapes with kaleidoscopic play of colors" [46, p. 15].

Hofmann later took a larger dose of LSD (5 times the typical psychedelic dose 0.1-0.3 mcg) to confirm that the drug had been responsible for his earlier experience because he doubted that very small doses of a drug could produce its dramatic effects [45]. His second experience was more intense and less pleasant than his first. Hofmann reported that his

> surroundings transformed themselves in more terrifying ways … [and] familiar objects and pieces of furniture assumed grotesque, threatening forms … A demon had invaded me, taken possession of my body, mind and soul ... and I was seized by the dreadful fear of going insane" (p16).

Hofmann observed that

> the last thing I could have expected was that this substance could ever find application as anything approaching a pleasure drug (p17).

Psilocybin was a psychedelic substance that Hofmann identified in mushrooms obtained by amateur ethnobotanist and psychedelic mycophile R. Gordon Wasson from indigenous Mexican healer María Sabina in 1955 [42,44]. Hofmann identified two psychoactive substances in the mushrooms, psilocybin and psilocin which he synthesised in 1958. In 1962 Hofmann travelled to Mexico with Wasson where he received personal confirmation from Sabina that in sufficient dosage the effects of synthetic psilocybin were indistinguishable from the mushroom [46]. Hofmann also isolated a naturally occurring derivative of lysergic acid in the seeds of a Mexican plant [46].

Hofmann's employer Sandoz took out patents on LSD and psilocybin. They were unclear what their medical uses may be and so made them available to psychiatrists and medical practitioners to explore their clinical uses and to use the drugs to better understand the psychotic experiences of their patients [46]. In the 1950s, clinicians could use unapproved drugs like LSD in their personal "clinical research" that was often undertaken in their routine clinical practice. Experimentation with a "promising" new drug, like LSD, often involved a psychiatrist taking a drug to test its effects before assessing its efficacy by giving it to their patients, who were usually long stay residents in large psychiatric hospitals.

5 Medical uses of psychedelic drugs

5.1 Mescaline and LSD as "model psychoses"

In the 1930s and 1940s, psychiatrists reported that the visual and cognitive effects of mescaline resembled the symptoms of schizophrenia and other psychoses [7,18,33] and conjectured that these disorders were caused by a "toxic amine" that chemically resembled mescaline [33]. In the early 1950s, Osmond and Smythies [47] hypothesised that adrenochrome, a derivative of adrenalin, was the cause of schizophrenia [5,48] because it had hallucinogenic effects [5,7] that could be reversed by large doses of vitamin B3 [49].

Other researchers were unable to isolate adrenochrome from the sera of persons with schizophrenia or to replicate the effects of niacin on psychotic symptoms [50]. There was stronger support for an alternative biochemical theory according to which psychotic symptoms in schizophrenia were caused by disturbed dopamine function [33]. In the 1950s heavy users of methamphetamine reported auditory hallucinations and paranoid delusions [51] and the drug chlorpromazine that reduced psychotic symptoms acted on the brain's dopamine system [52,53,54].

5.2 LSD treatment of alcoholism

In the late 1950s, Osmond and Hoffer used LSD to treat the large numbers of patients with alcohol dependence who were residents in the overcrowded mental hospitals of Saskatchewan where they worked [5,7,55]. They hoped that an effective drug treatment for alcoholism would reduce hospital overcrowding and convince the public that alcoholism was a "disease" rather than a moral weakness [6]. They initially assumed that large doses of LSD would produce psychotic symptoms like those that occur in delirium tremens (DTs) during alcohol withdrawal and that according to the lore of Alcoholics Anonymous (AA) 'scared' alcoholics into sobriety [5,6]. Instead, they found that LSD more often produced a mystical epiphany that led their patients to cease drinking [6].

Osmond used "psychedelic therapy" to describe the use of high doses of LSD to produce these mystical epiphanies [20] that he and Hoffer believed were essential for successful treatment. The mystical experiences facilitated engagement with Alcoholics Anonymous that helped to sustain their abstinence after discharge from hospital [5,6,56]. The Saskatchewan chapter of AA was very supportive of their approach [56,57], as was Bill Wilson, one of the founders of AA, whose own path to abstinence began with a mystical experience produced by scopolamine that he was given while undergoing alcohol withdrawal. Wilson thought that LSD experiences would facilitate entry to AA [9] but he was not able to persuade the AA fellowship to support this use because the majority opposed the use of any psychoactive drugs in the treatment of alcoholism [5].

Osmond used LSD to treat two severely alcohol dependent patients, both of whom were abstinent after 6 months. He and Hofmann then encouraged their younger colleagues to use LSD while they focussed their research on the aetiology and treatment of schizophrenia.

Their younger colleagues treated small groups of patients and reported 50% abstinence rates 6 to 12 months after treatment [5,6,55].

Sceptical colleagues in Canada and North America questioned their results [5,55,58]. First, they argued that these studies involved very small numbers of patients, there was no comparison treatment, and the treatment outcomes were assessed by the therapists only 6 months after treatment [59]. Second, they also disbelieved the 50% abstinence rates [5,7] because therapists were aware of the treatment that their patients had received and, the critics, claimed, the therapists' judgments were biased by their own LSD use [5,6,9]. One critic, Louis Jolyon West, commented that "either LSD is the most phenomenal drug ever … in psychiatry, or else the results were evaluated by criteria imposed by enthusiastic, if not positively prejudiced, people" (cited by [9]). Third, Osmond's claim that mystical experiences were essential for successful treatment did not fit with a scientific approach to identifying a specific drug to treat alcohol dependence [5,6,10].

Osmond and Hoffer's claims were called into question by the results of a randomised controlled trial of LSD. A study conducted at the Addiction Research Foundation in Toronto in the early 1960s compared the effects of an 800 mcg dose of LSD with ephedrine and treatment as usual on heavy drinking in alcohol dependent patients [5,55]. In this and other later trials, investigators reported substantial improvements in patients who received all of the treatments but outcomes were no better in patients who were given LSD [55]. Osmond and Hoffer argued that the ARF study had not evaluated their treatment approach because patients were only given a single very large dose of LSD, without any preparation of set or setting or psychotherapeutic support during the LSD experience, and received no aftercare [5].

The Saskatchewan Bureau of Alcoholism followed up 150 patients 2 to 60 months after they were given LSD treatment in the Province's hospitals. It reported an abstinence rate of 22% and recommended that the treatment be used in all of its hospitals [5]. LSD treatment of alcoholism, however, largely ceased in 1961 in Saskatchewan when a new provincial government proved unsympathetic to this treatment approach [5]. Osmond and his colleagues took up clinical and research positions elsewhere in Canada and the USA [5].

Later controlled studies more faithfully implemented Osmond and Hoffer's treatment model. These studies reported higher abstinence rates at 3 months in those given LSD but these differences had disappeared 12-18 months after treatment [5,55]. This included a study co-authored by Osmond [60] which concluded that follow up LSD treatment was necessary to extend abstinence beyond the 'LSD honeymoon' [5]. A meta-analysis of the five randomised controlled trials of LSD in alcohol dependence (with a median of 44 patients per trial) confirmed that the benefits of LSD treatment evident 3-6 months after treatment had disappeared by 12 months [61]. Another systematic review of these controlled trials also found that LSD treatment only produced short term improvements in patients with alcohol use disorders [62].

5.3 Psychotherapy for anxiety and depression and anxiety in terminal illnesses

Psychiatrists in Europe and North America used low doses of LSD to facilitate psychodynamic psychotherapy for anxiety and depressive disorders [18, p. 39]. In this treatment - described as psycholytic therapy – patients were given repeated low doses of LSD to enable the recovery and abreaction of unconscious traumatic memories that their therapists believed were the source of their disorders. In case series, therapists reported that 70% of their patients with anxiety and depressive disorders improved after receiving this treatment (e.g. [63]). In the 1970s, Kurland and colleagues in Maryland also reported good outcomes in clinical trials of patients with anxiety and depression who they treated with LSD and other psychedelic drugs [64]. Sceptics noted that the unconscious content revealed in this treatment often reflected the psychotherapeutic orientation of the therapist, with patients variously reliving birth traumas, recollecting early childhood sexual abuse or recovering material from the 'collective unconscious' (e.g. [63,65]; see [66] for a review).

In the late 1950s and early 1960s, physicians also gave LSD to terminally ill cancer patients with the aim of relieving their pain. They found that their patients reported psychedelic experiences which substantially reduced their anxiety and depression (e.g. [67,68,69,70]). Their experiences facilitated reconciliations with family members and increased patients' acceptance of their impending deaths [71]. As was the case with persons treated for addiction, many patients reported mystical experiences that their therapists believed were essential for positive treatment outcomes [25].

6 Nonmedical uses of psychedelic drugs

6.1 Psychedelic drugs and mystical experiences

The English intellectual, Aldous Huxley, was responsible for popularising the idea that psychedelic drugs could produce spiritual enlightenment after he took mescaline provided by Humphry Osmond in May 1953 [3,5,33]. Huxley's account of the experience in the Doors of Perception [72,73] increased interest in this use of psychedelic drugs and arguably provided the "set and setting" for many persons who subsequently used psychedelic drugs [3,18,21].

Huxley took mescaline in the hope of having a mystical experience, like those described by the English mystic William Blake, who provided the motto for his essay: "If the doors of perception were cleansed, everything will appear to man as it is, infinite" [73]:

> … I was convinced in advance that the drug would admit me, at least for a few hours, into the kind of inner world described by Blake … But what I had expected did not happen … no visions of many-coloured geometries, of animated architecture, rich with gems and fabulously lovely" (p15).
>
> The change …in the world was in no sense revolutionary … I became aware of a low dance of golden lights … [and] sumptuous red surfaces swelling and expanding from bright nodes of energy that vibrated with a continuously changing, patterned life (p16).

> I was seeing what Adam had seen in the morning of creation – the miracle, moment by moment, of naked existence" (p17).

Huxley believed that mescaline bypassed the "cerebral reducing valve" that enabled humans to function in everyday life. This expectation preceded his mescaline experience, as is evident in a letter he wrote to Osmond before his mescaline experience [74, p. 5] on 10 April 1953:

> It looks as though the most satisfactory working hypothesis about the human mind must follow, to some extent, the Bergsonian model, in which the brain with its associated normal self, acts as a utilitarian device for limiting, and making selections from, the enormous possible world of consciousness, and for canalizing experience into biologically profitable channels.

Huxley argued that mescaline was less harmful than alcohol and tobacco in producing "chemical vacations from intolerable self-hood and repulsive surroundings" [72, p. 53]. He believed that it could "relieve and console our suffering species without doing more harm in the long run than it does good in the short" [72, p. 53]. This was because it was "potent in minute doses and synthesizable … less toxic than opium and cocaine", had "fewer undesirable social consequences than alcohol or barbiturates" and was "less injurious to the lungs than tobacco". It produced "changes in consciousness more interesting, more intrinsically valuable than mere sedation, or dreaminess, delusions of omnipotence or release from inhibition". He argued that the long history of indigenous mescaline use showed that it was "completely innocuous" [72, p. 53].

In a later essay, Heaven and Hell, Huxley acknowledged that psychedelic experiences were not always pleasant [75, p. 109]:

> Visionary experience is not always blissful. It is sometimes terrible. There is hell as well as heaven … The user of a psychedelic drug, in particular, may experience either state, depending on the prior condition of his psyche … The torments of Dante's inferno are experienced by schizophrenics and persons who take mescaline and LSD under unfavourable conditions … Fear and anger bar the way to heavenly Other World and plunge the mescaline taker into hell.

After the mid-1950s, LSD replaced mescaline as the drug of choice for spiritual exploration. The dose required was measured in micrograms rather than milligrams, it produced fewer adverse physical effects than mescaline and it could be obtained for free from Sandoz [5]. Huxley, Timothy Leary, Richard Alpert (later known as Baba Ram Dass) and others were all introduced to LSD by Al Hubbard, reputedly a former bootlegger, CIA agent, and religious mystic who promoted LSD use for religious purposes to enlighten the governing elite [3,21,33]. The politically conservative publisher of Time and Life magazines, Henry Luce, advocated the use of LSD for spiritual enlightenment after being given the drug by Sidney Cohen, at Huxley's recommendation [21,44]. Luce's magazines published very positive stories on the religious use of LSD well into the mid-1960s [21]. The actor, Cary Grant, also gave LSD a celebrity endorsement [3] when he recounted his experiences with using it in psychotherapy in leading women's magazine Good Housekeeping in 1958. Some Silicon

Valley pioneers (including Steve Jobs and Bill Gates) used LSD and some of these pioneers later funded psychedelic research [18].

6.2 The counterculture's embrace of LSD

Timothy Leary's experience with magic mushrooms while on holiday in Mexico in 1960 is often seen as marking the beginning of the end of the legal use of psychedelic drugs. After returning from his holiday, Leary launched the Harvard Psilocybin Project that involved giving psilocybin and LSD to Harvard students and prisoners [3,21,44]. Leary left Harvard in 1963 after his colleagues in the Department of Social Relations complained about the quality of his "research" and the unsupervised use of LSD that his colleague Alpert encouraged among Harvard undergraduate students. Leary thereafter promoted the use of LSD as a religious sacrament [3,44] and in 1967 infamously encouraged young people to "tune in, turn on and drop out" [21].

Ken Kesey was another psychedelic evangelist in California who was an advocate of recreational psychedelic drug use [44]. After he was given LSD in a research study at Stanford University [33], Kesey began to promote its recreational use using the slogan: "freak freely". He and his "merry pranksters" travelled the USA in a school bus staging "Electric Kool-Aid Acid Tests". During these events participants drank the neon-coloured American powdered "family" beverage spiked with LSD and "tripped" to the music of the Grateful Dead [76]. Kesey is estimated to have given LSD to more young people in the USA during these "Acid Tests" than all academic LSD researchers during the period [44].

The well-publicised psychedelic advocacy of Timothy Leary, Ken Kesey, Alan Ginsburg and Hunter S Thompson [77], made LSD use a rite of passage in the "counterculture" [16]. Psychedelic drug effects were popularised in the music of The Doors (who took their name from Huxley's book) and the Beatles' 1967 album 'Sergeant Pepper's Lonely Hearts Club Band'. A ban on LSD in the mid-1960s in California generated its large-scale underground production that increased use and 'bad trips' and caused public alarm [39]. Nixon responded to the public alarm by including LSD in the US Federal Controlled Substances Act in 1970 where it was included in the same drug class as with heroin, cocaine and methamphetamine [3,21,33,44].

6.3 Morally questionable nonmedical uses of psychedelic drugs

Not all who experimented with LSD pursued spiritual wisdom. In the 1950s the US Army, for example, funded research on the potential use of LSD to disable enemy troops while the Central Intelligence Agency (CIA) conducted clandestine research on using LSD to interrogate foreign spies [44,78,79,80]. The CIA secretly funded psychiatric research on LSD-induced psychoses and conducted egregiously unethical research in which persons were given LSD without their knowledge or consent, a practice that led to at least one suicide [44,81].

Charles Manson notoriously used LSD to recruit young runaway women into his "Family" [13,15]. He later used LSD to convince his followers that he was the Son of Man ('Man-Son') and persuaded them to commit a series of gruesome murders in Los Angeles in 1969 in hopes of provoking a race war. His 1970 trial for these murders generated enormous national and international media publicity about the evils of LSD. The trial was said by some to mark the end of the 1967 "summer of love" [15,82,83].

In Australia, charismatic yoga teacher Anne Hamilton-Byrne used LSD as a source of authority in founding a cult known as "The Family" in the 1970s and 1980s. Hamilton-Byrne dosed potential recruits and followers with this drug to reinforce her claims to be the reincarnation of Jesus Christ. She illegally "adopted" the children of her followers and single mothers and subjected these children to physical and emotional abuse, including the coerced use of LSD [84,85].

In the late 1960s and early 1970s, UCLA anthropology student Carlos Castaneda [86,87] published a series of best-selling books that became staples of the counterculture. He claimed to be relaying lessons from Don Juan, a Yaqui medicine man, on how to use psychedelic plants, such as peyote, to access an "alternative reality" [33]. Castaneda was later shown to have plagiarised ethnographic research on different indigenous groups in the Americas, including groups with no history of using psychedelic plants [33,86,87].

The Weathermen, also known as the Weather Underground, was a group that aimed to bring down the US government by committing acts of "revolutionary violence" that included robbing banks, bombing government buildings, and killing police officers [80]. They used LSD to reinforce group cohesion and expose possible FBI informers. They also helped Timothy Leary to escape from a California prison after he was sentenced for marijuana possession in 1970 [88].

7 Why was research on the psychedelics abandoned in the USA?

The passage of the Controlled Substances Act (CSA) in 1970 is often regarded as marking the end of psychedelic research in the USA because it included psychedelic drugs in the same schedule as heroin, cocaine and cannabis as drugs with high abuse potential and no medical use [21]. According to the popular account, Richard Nixon used the advocacy of Leary, Ginsberg and Kesey to justify the inclusion of LSD in Schedule 1 of the CSA [8,83]. Nixon did play a role in the prohibition of LSD use, but recent historical scholarship provides a more complicated explanation of when, how and why research on the therapeutic use of psychedelic drugs ended [6,17,89].

7.1 New pharmaceutical regulations

A major reason for the decline in psychedelic research was an event that occurred seven years before the enactment of the Controlled Substances Act. This was the passage in 1962 of legislation that tightened the regulation of research on new pharmaceutical drugs by the Food and Drug Administration (FDA) [10,11,90]. The legislation was prompted by the

Thalidomide tragedy that occurred when physicians in Europe and Australia used thalidomide to treat morning sickness in pregnant women (in the absence of evidence on its safety in pregnancy), producing an epidemic of the severe birth defect, phocomelia [91].

Before 1963, clinical research on new drugs was largely unregulated. Any clinician could use an unapproved drug for "research" in their routine clinical practice without the need for a clinical trial protocol or ethics committee approval [90]. This was how research had been done on lithium in the 1940s, and on chlorpromazine, tricyclic antidepressants, and LSD in the 1950s [52,83].

The new FDA regulations ended these practices [10,11]. Clinical research now required a formal Clinical Trial Notification (CTN) that included a dossier of preclinical evidence showing that the drug was safe and likely to have therapeutic value. It also required a study protocol for a double blind randomised controlled trial (RCT) that would assess the drug's safety and effectiveness [10]. Research on psychedelics came under these regulations because there was limited evidence at this time on their safety and efficacy from controlled clinical trials [10,11,90].

Leary's advocacy of nonmedical psychedelic use made it more difficult to conduct clinical trials on LSD. In 1965, Sandoz decided that it would no longer provide LSD to clinical researchers because media reports of psychoses, accidental deaths and suicides attributed to LSD were damaging the company's reputation [46]. Sandoz continued to supply LSD to US researchers who worked in universities and hospitals and whose research was funded by the National Institute of Mental Health and the Veterans Administration [10].

7.2 Calls for tighter regulation of medical use of LSD

Well before the CSA was passed, leading US medical professionals advocated for tighter controls on the clinical use of psychedelic drugs because of the ways some therapists were using LSD [9]. In the late 1950s, for example, Sidney Cohen, a psychiatrist at UCLA who used LSD in psychodynamic psychotherapy, reported psychoses and suicide attempts among patients given LSD by private therapists in Los Angeles. In Cohen's view, these therapists included "an excessively large proportion of psychopathic individuals" (cited by [9]). He advocated tighter controls over the medical use of psychedelics because he feared that their inappropriate use would bring a potentially useful psychiatric treatment into disrepute [92].

7.3 Psychedelic research after 1970

Contrary to popular belief, clinical research on psychedelic drugs did not end in 1970 with the passage of the CSA [10]. The FDA continued to support, and NIMH continued to fund, clinical research on psychedelic drugs into the mid-1970s [10]. The State of Maryland funded clinical research on psychedelic drugs at the Spring Grove Hospital until 1979. This research included clinical trials of psychedelics in the treatment of alcohol dependence, neurotic disorders and anxiety in terminal illness [64,69]. The short-term results in these trials were positive but less impressive than the results reported by Osmond and Hoffer and other early

researchers [12,64]. The research came to an end in 1979 when the Maryland government terminated the group's funding for a variety of reasons. These included public disquiet about LSD research after a Congressional inquiry into Army and CIA research (some of which was conducted in army bases in Maryland), and conflict within the research group that prompted an external review of its funding recommending it be reallocated to research on schizophrenia [12].

Academic research on psychedelic drugs also declined for another under-appreciated reason. Researchers became increasingly concerned that their reputations would be damaged if they did research on these drugs because they risked receiving some of the adverse media publicity generated by Timothy Leary and the counterculture use of these drugs [55]. Senior researchers reportedly advised younger researchers against doing research on psychedelic drugs because of the reputational risks [55].

The changing attitudes towards these drugs was reflected in the changing tone of scientific publications on LSD. Human studies published in biomedical journals indexed by the US National Library of Medicine from 1955-1995 were generally very favourable until around 1968 after which the number of unfavourable reports greatly outnumbered the favourable ones [93]. Abraham et al argued that this pattern exemplified the typical biphasic pattern of research on new pharmaceuticals: initial enthusiasm accompanied by uncritical reporting of positive outcomes, followed by growing disillusionment as doubts grew about the validity of the therapeutic claims and the number of adverse events reported increased [93].

8 The revival of research on psychedelic drugs in the 1990s

8.1 Reasons for the revival

The US Congressional Joint Resolution and the Presidential declaration of the 1990s as the 'decade of the brain' helped to legitimise research on psychedelic drugs whose effects promised to increase our understanding of the neurobiological bases of consciousness and mental disorders [18]. Animal research explored the mechanisms of action of psilocybin in the USA in 1994 [94]; in the late 1990s in Switzerland, human laboratory studies examined the psychological and cognitive effects of psilocybin [95]. The first US study of the effects of psilocybin on mystical experiences was published in 2006 [3]. Bob Schuster, a former Director of the US National Institute on Drug Abuse (NIDA), played a key role in persuading psychedelic researchers in the USA to conduct clinical trials on psilocybin as well as introducing the lead researcher, Roland Griffiths, to a philanthropist who funded the research [3].

The revival of clinical psychedelic research appears to have been the result of several factors. A major driver was the determination of a small group of researchers and clinicians to undertake research (see text box) because they believed that psychedelic drugs had an important role in treating common psychiatric disorders such as depression and anxiety [96,97,98,99]. Some of these individuals, who had strong track records in

psychopharmacological and neuroscience research on drugs, formed a network of researchers in the UK, USA and Switzerland [3,18].

Box 1: Some leading psychedelic researchers and their supporters

Rick Doblin made it his life's mission to secure regulatory approval for the medical use of psychedelic drugs [100] and raised philanthropic funds for clinical trials of MDMA-assisted psychotherapy in post-traumatic stress disorders [101].

David Nichols is a medicinal chemist who established the Heffter Research Institute in 1993 to conduct research on the actions and therapeutic uses of psilocybin [98].

Roland Griffiths is a psychopharmacologist who conducted the first trial of the capacity of psilocybin to "reliably occasion" spiritual experiences [102].

Amanda Feilding has advocated for and raised funding for neuroscience and clinical research on psychedelic drugs [103].

Franz Vollenweider is a Swiss psychiatrist who conducted human studies of the neuropsychological effects of psilocybin in the late 1990s [95].

Around the time of the research revival, historians also began to publish accounts of North American research on psychedelic drugs in the 1950s and 1960s based on extensive archival research (e.g. [6,21]). These historians sympathetically situated the early research in its time and place and showed that it was similar in quality to contemporaneous research on psychotropic drugs that are still used to treat depression, anxiety and schizophrenia [5,12,52]. Some argued that these histories showed that a promising treatment had been prematurely abandoned because of a societal panic about LSD use in the counterculture and sensationalised media stories about its adverse effects [5,6,21].

Systematic reviews of the early psychedelic clinical research published around the same time also provided more positive assessments of patient outcomes of early psychedelic treatment [25,55,61,62,101,104]. Authors of these reviews argued that the results of the early small sample trials showed that more rigorous, larger clinical trials were warranted on the use of psychedelics to treat addiction, depression and distress in terminal illness.

8.2 Continuities in psychedelic research

Contemporary psychedelic researchers followed the example of their predecessors (e.g. [101]) in investigating the therapeutic use of psychedelic drugs in treating alcohol and drug dependence, depression and anxiety, and distress in patients with terminal cancer [25,71,97,104]. Their clinical trials were largely funded by philanthropic sources because it had been difficult to secure government funding [1,18]. The pharmaceutical industry was also not interested in funding trials of LSD and psilocybin because both drugs were off patent.

Bob Wallace, a Silicon Valley philanthropist, funded Heffter's research and Roland Griffiths received funding from Bob Jesse and John Gilmore, two Silicon Valley philanthropists, whose goal was to secure FDA approval of a psychedelic drug for medical use [18]. David Nutt has received funding from the estate of Max Mosely, the former CEO of Formula One racing [105]. The reliance on philanthropic funding was an interesting continuity with earlier research because Leary also received funding from wealthy Americans and the not for profit sector in the 1960s [106].

For-profit companies began to fund psychedelic drug research after the positive results of the phase 2 trials of MDMA and psilocybin and the FDA's decision to designate psilocybin and MDMA as potential breakthrough drugs for depression and post-traumatic stress disorder (PTSD) [26]. In 2020, COMPASS Pathways patented a process to synthesise psilocybin and MindMed became the first publicly listed company developing psychedelic therapies on a Canadian stock exchange [107]. Some clinical researchers have argued that this investment puts the cart before the horse in assuming that these treatments are safe and effective [108]. The advent of for-profit companies has not been welcomed by some psychedelic advocates who fear that these companies will seek to maximise profits by using their patents to restrict access to psychedelic assisted therapies while marketing psychedelics broadly for off-label use [109,110,111,112].

8.3 Differences between recent and earlier psychedelic research

Psychedelic research in the 21st century has been undertaken by researchers in major research universities in the USA, the UK and Europe; the early psychedelic research consisted of largely uncontrolled clinical series conducted in state mental hospitals [6,12]. Current investigators are trained in psychopharmacology and in conducting clinical trials of new treatments; the early investigators were primarily clinicians who treated large numbers of patients with chronic mental disorders in overcrowded public mental hospitals.

Contemporary researchers have conducted randomised controlled clinical trials to the standard required for approval by medical regulators, such as the FDA in the USA [26,101,113]. Randomised controlled clinical trials were in their infancy in the 1950s and 1960s and many of the early psychedelic investigators (e.g., Abramson, Osmond and Hoffer) argued that randomised controlled trials were not an appropriate way to evaluate the effectiveness of psychedelic treatments because patients needed to be prepared for and be made aware of which drug they would receive [6].

Another difference has been in the choice of psychedelic drugs to investigate. Contemporary clinical researchers have chosen psilocybin rather than LSD, the drug most often used by earlier researchers. Psilocybin's pharmacology has been a major reason for the choice. It has a shorter period of action (4-6 hours) than LSD (8-12 hours) and its pharmacology is better understood. It is less likely to produce "bad trips" and lacks the countercultural baggage of LSD [3]. Clinical trials have also been conducted on the efficacy of MDMA-assisted psychotherapy in PTSD [114]. Some researchers have conducted open label clinical studies of plant-based psychedelic drugs, such as, ayahuasca and ibogaine [115].

Contemporary psychedelic researchers have also distanced themselves from the advocacy of Timothy Leary by publicly advising against the nonmedical use of psychedelics. Rick Doblin excepted, they have not publicly disclosed whether they have had any personal experiences with psychedelic drugs [3]. Osmond and Hoffer, by contrast, enthusiastically described their mescaline and LSD experiences, encouraged doctors and nurses in their hospitals to take the drug, gave LSD to journalists and reported taking LSD with their patients [116].

9 How safe are psychedelic drugs?

9.1 Acute adverse effects

No fatal overdoses have been reported among persons who have used psychedelic drugs [71]. The estimated human lethal dose of LSD (based on animal studies) is 100 mg, an order of magnitude greater than the typical psychedelic doses of 200-400 micrograms. Eight individuals have survived after taking larger doses of pure LSD intranasally in the mistaken belief that it was cocaine [71]. US coroners have attributed a small number of deaths to LSD but Nichols has argued that these deaths are more likely to have been cardiovascular deaths in heavily intoxicated persons who were forcibly restrained by the police [71].

Adverse events were rarely reported by patients who were given LSD under medical supervision in the late 1950s in the USA [92] or in the 1960s in the UK [117]. Adverse events may not always have been reported, however. Doblin discovered in a 20 year follow up [118] of Pahnke's Good Friday experiment [119] that one of the 10 subjects given psilocybin developed psychotic symptoms that were treated with an antipsychotic drug.

"Bad trips" were more common among naïve nonmedical users of LSD in the mid to late 1960s [92,120,121]. Anxiety was the most common symptom that could usually be managed by "talking down" users [120,121]. Small numbers of psychoses and suicides were reported (but it was often difficult to decide whether these were attributable to psychedelic drugs or other illicit drugs, or symptoms of pre-existing psychotic disorders [39,120]). There were a small number of accidental deaths in individuals who jumped or fell from buildings after taking LSD [39].

A 1968 study of chromosome damage in mice given LSD [122] may have contributed to the ban on LSD because it came soon after the Thalidomide tragedy [21,39]. Better controlled studies in human LSD users did not support this finding [123,124] but these studies were published well after LSD had been banned [21].

Very few adverse events were reported among the estimated 31 million persons who used psychedelic drugs for recreational reasons in the USA in the 2010s [125]. Very few presented to emergency departments for problems related to psychedelic use and even fewer were treated in mental health or addiction treatment services [125]. A review of adverse effects reported by recreational users of psychedelic mushrooms in the Netherlands found low rates of adverse effects, very few of which required medical attention, and no evidence of a dependence syndrome [126]. In population surveys in the USA, persons who have used LSD

report better mental health on average than persons who used other illicit drugs [125]. It is difficult, however, to exclude the possibility that this is because young adults in good mental health are more likely to use psychedelics than other illicit drugs.

Studerus et al [127] reported the prevalence of short-term adverse effects among 110 persons who were given psilocybin in laboratory studies. A third of their sample experienced marked anxiety that was dealt with by reassurance within the session. Most of the other adverse effects were minor: fatigue, headaches, lack of energy, and difficulty concentrating the day after taking the drug. Eleven reported "negative changes in psychological well-being and/ or mental functions" after the psilocybin session but these were generally transient. There was a similar prevalence of marked anxiety (40%) in a recent trial of psilocybin in the treatment of major depressive disorder [128].

9.2 Long term adverse effects

There are limited data on the longer-term adverse effects of psychedelic drugs. These come from studies of highly selected participants in laboratory and clinical studies that excluded persons with psychiatric disorders [2]. Aday et al [129] systematically reviewed the adverse events reported a month after taking a psychedelic drug among 2000 people who participated in 34 studies between 2006 and 2016. Psilocybin was the drug most often used (28 studies, 5 LSD and one of ayahuasca). Participants included persons treated for intractable depression (10 studies), healthy volunteers (9 studies), patients in end-of-life distress (7 studies), and tobacco users (4 studies). A third of their participants reported increased anxiety in the session that required reassurance, but this symptom did not persist after treatment.

Studerus et al [127] also reported on longer-term adverse effects of psilocybin in 110 persons 8-16 months after they participated in laboratory studies that involved taking psilocybin. One reported "persistent emotional instability, anxiety and depressive feelings" that he attributed to the release of "suppressed memories". He recovered after psychotherapy [127]. This is an approximate 1% rate of persistent adverse events that may under-estimate the prevalence of adverse symptoms in unselected participants because Studerus et al excluded subjects with a history of psychoses, depression and anxiety, and 40% of their subjects had used hallucinogens, 20% more than 10 times.

9.2.1 Hallucinogen persisting perception disorders

Sandison and Whitelaw [130] reported that some patients who received LSD assisted psychotherapy reported a recurrence of the perceptual effects of LSD after the end of intoxication, a phenomenon referred to as psychedelic "flashbacks". Victor [131] defined these as "the transient recurrence of psychedelic drug symptoms after the pharmacologic effects of the drugs have worn off".

ICD-10 included a hallucinogen persisting perception disorder within the category of hallucinogen dependence [132]. The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) published by the American Psychiatric Association [133] includes a diagnostic category of hallucinogen persisting perception disorder (HPPD) that is defined by

the recurrent perceptual disturbances arising from the use of hallucinogenic drugs. Two types of HPPD were proposed by Halpern et al [134]. Type 1 describes persons who report infrequent and transient symptoms. Type 2 includes persons who report more persistent symptoms and significant impairment and distress.

The evidence for HPPD comes primarily from case studies and case series [134], making it difficult to estimate its prevalence among persons who use psychedelic drugs [2,134]. A recent literature search by Vis et al [135] that imposed no time limit on reports and included articles in a range of languages other than English identified 66 papers that collectively described 97 cases whose symptoms met the criteria for HPPD. This suggests that the prevalence of HPPD is very low, given that multiple millions of persons are estimated to have used psychedelic drugs over the period covered by their review [134].

A recent prospective study reported the prevalence of recurrent psychedelic symptoms or flashbacks among persons who were given LSD and psilocybin in laboratory studies [136]. They found that 13 of their 142 participants reported some perceptual experiences in the days to weeks after study participation. Only one, however, reported that these symptoms persisted during a 30 month follow up. None found their symptoms distressing or impairing and so none met criteria for a DSM-5 diagnoses of HPPD type 2. Again, a major caveat is that 30% of these participants had prior experience with psychedelic drugs.

Not all psychedelic drugs may be as benign as LSD and psilocybin. A recent study reported 58 case reports of flashbacks among persons who had used the synthetic hallucinogen 251-NBOMe for recreational purposes [137]. In 15 cases, symptoms persisted for some months after last use and this was most common in those who used the drug several times a month [137].

9.2.2 Abuse and dependence potential

Johnson et al [138] assessed the abuse potential of psilocybin against the criteria used to assign drugs to Schedule 1 of the US Controlled Substances Act (CSA), a classification given to drugs with a high abuse potential and no medical uses. Johnson et al argued that psilocybin has a very low abuse potential because it does not produce euphoria in humans, and animals do not self-administer it. Psilocybin is much less regularly used than cannabis, cocaine and opioids in population surveys and problems related to hallucinogens are rare among persons seeking medical help for acute adverse effects of drug use or wanting treatment for problems related to their drug use. A recent review of the adverse effects of psychedelic drugs by Schlag et al came to the same conclusion on dependence and abuse potential for the same reasons [137].

Johnson et al argue that psilocybin also poses a low risk to public health because users rapidly develop tolerance and do not persist in using it. Similar arguments can be made more generally about other psychedelic drugs such as LSD. Tolerance to their effects develops rapidly, there are no withdrawal symptoms on cessation of use and very few people seek treatment for dependence on these drugs, despite widespread recreational use in the USA during the 2010s [125].

9.3 The potential risks of heightened suggestibility under psychedelic drugs

A common effect of psychedelic drugs is heightened suggestibility both during and immediately after the drug experience [139,140]. This is reflected in the importance that therapists place on creating an appropriate "set and setting" to produce a psychotherapeutic or mystical experience and to avoid bad experiences [141,142]. Hartogsohn has described LSD as a "pharmacological chameleon" because it "changes its psychedelic pigmentation in response to the cultural settings in which it is used" in ways that "magnify and amplify the content of one's experience". In the hands of unscrupulous persons, this property of psychedelic drugs can be used for malign purposes, as Shortall [143] argued was the case with the US Army and CIA's attempts to use psychedelic drugs as weapons of war and spycraft. This misuse of psychedelic drugs is also exemplified by the those who have used them to form cults, such as, Charles Manson and Anne Hamilton-Byrne.

Timmermann et al [144] have recently shown that psychedelic drugs can change the metaphysical beliefs of study participants. They argue that study participants should be fully informed about this possibility if they are to give fully informed consent to participation in research on psychedelic drugs. Smith and Sisti [145] have argued that, for much the same reason, persons who receive psilocybin-assisted psychotherapy for depression should be informed about the ego-dissolution effects of the drug.

More recently, Langlitz [142] and others have reported that right wing extremist organisations in Europe have used psychedelic drugs to recruit young people [142,146,147]. In light of these reports, and other evidence regarding the "cultural plasticity and political pluripotency" of the effects of psychedelics [148], Langlitz et al [142] have argued that we urgently need "moral inquiries" into the uses of psychedelic drugs.

9.4 Therapeutic Enthusiasms

The startling effects of psychedelics are not solely a risk to patients and research participants. What Pollan has described as an "irrational exuberance" can afflict persons who use psychedelics to treat patients [3]. Jay Stevens in his history of psychedelic drug use in the USA in the 1960s noted that: "Everywhere you looked therapists were turning into lower case gurus, with adherents rather than clients" [44, p. 255]. Concerns about these outcomes have recently been expressed by leading psychedelic researchers. Matthew Johnson, for example, has recently counselled psychedelic researchers and clinicians against becoming "gurus" to their patients and their research participants [140]. In 2020, Anderson et al [149] warned against the field repeating the "enthusiasms and fervent portentiousness" that led to the termination of early psychedelic research. They described worrisome signs of a "similar collective enthusiasm" in contemporary psychedelic psychiatry and advised

> caution when evaluating the judgement of research and clinical colleagues who have only begun to take psychedelics within the past couple of years … [because] grandiosity can loom large with initial psychedelic experiences, leading even conservative individuals to become wildly enthusiastic about the potentials of psychedelics to heal and transform.

10 Evaluating the effectiveness of psychedelics for medical use

A major challenge in conducting double blind randomised placebo-controlled trials of psychedelics is that their unique perceptual and other effects make it difficult to conceal from participants when they have received a psychedelic drug [5,57]. Contemporary models of psychedelic-assisted psychotherapy also emphasise the need to create an appropriate therapeutic set and setting to ensure that patients are well prepared for the experience to achieve the best clinical outcomes [4,150].

Contemporary clinical research studies on psychedelic drugs [151] have addressed these challenges by using either an "active placebo", such methylphenidate or dextroamphetamine, that has psychoactive but not psychedelic effects, or by using low, moderate and high doses of the psychedelic drug under study (e.g. psilocybin or MDMA) to see if treatment effects are dose-related [101,152,153]. In clinical trials, investigators also standardise the set and setting and manualise the psychotherapy given with the drug.

These strategies are unsuccessful in that most participants and therapists in the trials were able to correctly guess which treatment the person had received [2]. Burke and Blumberger [154] have argued that for this reason these designs bias trial results in favour of psychedelic drugs. Specifically, they argue that patients who knowingly receive the psychedelic-assisted treatment will experience a powerful placebo effect, in addition to any specific effects of the drug. Patients given the nonpsychedelic drug, or a low dose psychedelic drug, by contrast, will experience disappointment upon realising that they have not been given the psychedelic drug [155]. The FDA has nonetheless accepted these clinical trial designs as evidence for safety and efficacy.

In the absence of credible double-blind conditions, treatment outcomes from psychedelic drug treatments will need to be assessed as objectively as possible by researchers who are unaware of which drug participants have received. Ideally, treatment outcomes should be assessed at least 12 months after treatment so that any placebo effects – the LSD honeymoon of Cheek et al [60]– have dissipated and any specific effects of psychedelic-assisted therapy measured [26]. Trials should also compare the effects of psychedelic assisted treatments with first line treatments for the condition under study, as has recently been done with MDMA in PTSD and psilocybin in depression (see below).

10.1 How effective is psilocybin in treating anxiety and depression?

The effects of psilocybin in treating anxiety and depression in terminally ill patients have been evaluated in a small number of studies with small patient numbers [156]. All reported substantial reductions in the severity of depression and anxiety using standardised symptom scales [2,156,157]. Meta-analyses of these studies have found substantially larger reductions in depression and anxiety in the patients who received psilocybin than those in the control condition, with large effects sizes of more than one standard deviation [158,159].

The median sample size in these trials was 27 [158] and many used cross-over designs which makes subject blinding impossible [156]. In some studies, it is also unclear whether the persons who assessed treatment outcomes were aware of the treatment that the person had received [158,159]. One long-term follow up of 16 patients reported that treatment benefits were still present 3.2 to 4.5 years after treatment [160]. These results prompted the FDA to designate psilocybin a "breakthrough drug" for depression to encourage larger clinical trials.

In these studies, psilocybin often elicited a spiritual experience that was associated with a therapeutic effect in depressed patients with terminal illnesses [161]. Patients reported that their mystical experiences reduced their fear of death, reassured them of the love of their family and friends and convinced them of life's "goodness" [162]. Some suggest that the experience of ego loss reduces a person's anxiety about their impending death [18].

10.2 Psychedelics and severe depression

The effectiveness of psilocybin in depression was assessed in a randomised controlled trial with 12 patients given either a low or a high dose of the drug with supportive psychotherapy. There were very substantial reductions in depression in the patients who received the high dose, with 58% reporting a greater than 50% reduction in depressive symptoms at 3 months and this was maintained at six months [157]. An open label study of ayahuasca in six patients with major depression also found an 82% reduction in depression self-ratings between baseline and three weeks after treatment [157].

Carhart-Harris et al [163] reported a randomised double-blind controlled trial that compared the effectiveness of psilocybin and the SSRI antidepressant, escitalopram, in patients with depression. A total of 59 patients were assigned to one of these treatments (30 to psilocybin and 29 to escitalopram). The former group received two doses of psilocybin and a daily placebo while the other was given a low dose of psilocybin and daily doses of escitalopram. Outcomes were evaluated at six weeks using a depression inventory. The two-point difference on the primary study outcome between psilocybin and escitalopram on a depression symptom score, was not statistically significant but the psilocybin group performed better than the escitalopram group on secondary outcome measures. For example, more patients in the psilocybin group met criteria for a clinically significant remission in depression than did those who were given the escitalopram (57% and 28% respectively). Because they did not correct for multiple comparisons on the secondary outcomes, the authors acknowledged that larger and longer clinical trials were needed to robustly compare the effectiveness of escitalopram and psilocybin in treating depression.

10.3 MDMA and Post Traumatic Stress Disorder

Doblin and colleagues have conducted a series of small sample, phase 2 trials of the effectiveness of MDMA-assisted psychotherapy in PTSD. They chose to treat PTSD firstly because it is common among those who have served in the military, members of law enforcement agencies, and sexual assault survivors, and secondly because in a substantial

proportion of cases, PTSD does not respond to pharmacological interventions, such as, SSRI antidepressants [164,165].

In the trials of MDMA-AP for PTSD the patients were given MDMA along with intensive psychotherapy over several weeks. Initially, 3-5 hours of psychotherapy were given before MDMA was administered to build rapport and prepare participants for the MDMA sessions. Three MDMA-assisted sessions were supervised by male and female co-therapists who supported patients during the drug experience. Then there were several sessions of psychotherapy to work through and integrate the psychological material produced during the MDMA sessions. The FDA decided that the results of three small sample phase 2 trials were sufficient to give fast track status to MDMA-assisted psychotherapy. It has also allowed early compassionate access to MDMA-AP for 50 patients with PTSD who did not meet the inclusion criteria for the clinical trials [114].

In meta-analyses of these trials, the patients who received doses of MDMA of 100 mg had greater reductions in the severity of their PTSD symptoms than patients who were given a low dose of MDMA or psychotherapy without a drug [114,158,166]. There were large reductions in symptom severity between the start and end of treatment and additional improvement during the follow up, with the percentage of patients who no longer met diagnostic criteria for PTSD increasing from 56% to 67%. Most patients reported improved personal relationships and well-being; only a minority reported acute adverse drug effects.

In a systematic review of these studies, Feduccia et al [114] found that MDMA-AP produced equivalent reductions in symptoms to first line exposure-based psychotherapies. The effects of MDMA-AP were substantially larger than the two SSRI antidepressants the FDA has approved to treat PTSD. Patients who received MDMA reported fewer adverse side effects and lower treatment drop out than patients who were treated with SSRI antidepressants. There was a lower rate of drop out in the MDMA-AP patients despite this treatment requiring much more patient time than taking an antidepressant each day.

These trials share limitations of the trials of psilocybin. All had small patient samples (median of 18) and patient recruitment was highly selective because anyone with a history of the mental disorders that are often comorbid with PTSD such as, major depression and substance use disorders was excluded. The trials were also conducted by MAPS, an organisation that has advocated for psychedelic treatment of PTSD [158]. We would have greater confidence if these results were to be reproduced by investigators who are less committed to psychedelic therapies for PTSD.

Mitchell et al [165] recently addressed some of the limitations of the earlier trials. They conducted a randomised, double-blind, placebo-controlled, multi-site phase 3 clinical trial that tested the efficacy and safety of MDMA-assisted therapy in patients with severe PTSD. Their sample included persons with comorbid mental disorders, such as dissociation, depression, a history of alcohol and substance use disorders, and childhood trauma. After psychiatric medication washout, 90 participants were randomised in equal numbers to manualised therapy with MDMA or with placebo. The MDMA treatment included three preparatory and nine integrative therapy sessions. PTSD symptoms were measured with the

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5, the primary endpoint), and functional impairment was measured with the Sheehan Disability Scale (SDS, the secondary endpoint). Patients were assessed at baseline and 2 months after the last session. Adverse events and suicidality were tracked throughout the study. MDMA produced a larger reduction in the CAPS-5 score compared with patients in the placebo treatment and a significantly decrease on the SDS total score. MDMA did not induce adverse events or abuse, or suicidal thoughts.

10.4 Psychedelics and other mental disorders

Bogenschutz et al [104] reviewed a small number of open label trials with small samples that provided early assessments of the effectiveness of psychedelic drugs in treating alcohol, tobacco and heroin dependence. They described the results as "encouraging" and argued that larger controlled clinical trials were warranted. There are also studies suggesting that psychedelics may be useful in treating other psychiatric conditions but these involve very small patient samples, rarely used a comparison treatment, and were often open label so that both patients and treatment staff know which drug the patient was given [129].

10.5 Limitations of psychedelic drugs trials

The recent clinical trials of psilocybin, MDMA and other psychedelic drugs share the limitations of early trials of any new drug treatment for a mental disorder, namely, they involved very small samples of highly selected patients (screened to exclude those at high risk of adverse outcomes) and treatment was provided by well-resourced, enthusiastic and committed staff [2]. For these reasons, early studies of new treatments for chronic diseases typically report much better outcomes than are reported in subsequent larger clinical trials of unselected patient samples [167]. The results of the larger clinical trials are also typically a great deal better than those achieved after the drug is used in routine clinical practice.

This may be for several understandable reasons. The early studies are often conducted by researchers who are committed to the new treatment and fastidious in faithfully implementing it. They often select patients in ways that bias outcomes in favour of the new treatment, e.g., by ensuring low rates of comorbid conditions and recruiting patients who actively seek out the new treatment. The hope and hype that accompanies the trial of 'promising' new treatments for a refractory mental disorder may amplify placebo responses. For this reason, scepticism is warranted about claims that psychedelics are "on course to become the next major paradigm shift" or that they comprise "the first significant innovation in mental healthcare since 1987 when antidepressants were first introduced" [2,107]mailto:.

11 The mechanisms of action of psychedelic-assisted psychotherapies

The new psychedelic therapies, like their predecessors, are a form of psychedelic-assisted psychotherapy rather than simply a drug treatment. In Osmond and Hoffer's research on alcoholism, LSD was used to facilitate entry to Alcoholics Anonymous groups that were

intended to sustain abstinence. In psycholytic therapy, low dose psychedelic drugs were used to facilitate psychodynamic psychotherapy that explored the traumatic origins of the patients' mental disorders.

We know more about the acute mechanisms of action of the classic psychedelic drugs LSD and psilocybin than we do of how they facilitate the psychotherapies that accompany them. These drugs are 5HT-2a partial agonists and their effects are attenuated when a 5HT-2a receptor antagonist is administered [168]. Different drugs within the class of the psychedelics have different effects on a range of other 5HT receptors, and they may also act on other major neurotransmitter systems, such as dopamine [168].

Human neuroimaging studies of psilocybin have reported that it disrupts the resting "default mode network" (DMN) of the brain and increases connectivity between brain regions that do not usually communicate [25,71]. Aday et al have suggested that resetting the DMN increases open-mindedness, creates a sense of well-being and, in the case of patients who are terminally ill, promotes an acceptance of mortality. As noted, psychedelic drugs also enhance patients' responsiveness to therapeutic suggestions making therapists' advice seem more compelling. This may be a great positive in the hands of skilled therapists but enhanced suggestibility can also be misused by morally unscrupulous or poorly trained therapists [129].

Some researchers suggest that the mystical experiences are a causal factor in good outcomes because they produce "a sense of unity of all people and things accompanied by a sense of reverence and the authoritative truth value of the experience" [25, p. 92]. It is unclear whether these experiences play a causal role in recovery or whether they are a phenomenological marker of the patient having received a therapeutic dose [96]. Nutt et al [96] suggest that the causal role of mystical experiences could be tested by assessing whether psilocybin has therapeutic effects on depression when administered under a general anaesthetic. Alternatively, clinical trials could be conducted on the antidepressant effects of 5HT-2A agonists that do not produce psychedelic effects [27].

Other neural mechanisms have been suggested as potential explanations of psychedelic therapeutic effects. These include anti-inflammatory effects on neurons and the promotion of neurogenesis in the hippocampus and amygdala, brain regions that play a role in memory and emotional regulation [71].

Nutt et al [96] claim that psychedelic drugs "cure" rather than palliate depressive symptoms like SSRI antidepressants. Two doses of psilocybin, for example, immediately produce substantial reductions in depressive symptoms that have been sustained for 6 to 12 months in follow up studies. The SSRIs, by contrast, typically take two weeks to produce a therapeutic response and they appear to dull feelings, and patients may need to take these drugs for months or years. Nutt et al argue that psychedelic drugs facilitate insight and emotional release when given in conjunction with psychotherapy to produce "a healthy revision of outlook and lifestyle" [96, p. 24] Bender and Hellerstein [2] argue that this is a large claim to make on the basis of short term follow ups of small numbers of patients.

The contribution that the type of psychotherapy makes to patient outcomes is also unclear. We do not know whether MDMA assisted treatment for PTSD requires multiple session

psychodynamic psychotherapy by a male and a female therapist. MDMA, for example, could potentially be combined with the first line psychological treatments or PTSD, namely cognitive behaviour therapy and exposure-based psychotherapies [26]. Psilocybin could be used with cognitive behaviour therapy to treat depression and ensure that treatment benefits persist.

12 How likely are psychedelics to enter medical use?

12.1 Psilocybin for depression

If the positive findings in phase 2 trials are replicated in phase 3 trials, psilocybin will probably be approved to treat depression that has failed to respond to SSRIs. If approved for this indication, psychiatrists will have to manage demands from patients to use it to treat all forms of depression, given the popular media depiction of these drugs as a "disruptive treatment" that produces an immediate, clinically significant response that may be sustained for up to 12 months [96]. This claim makes it a much more attractive treatment than taking the SSRIs that require 2 weeks of treatment before any benefits are experienced and during which patients may experience unpleasant side effects [71,96].

If psilocybin is approved, there will be demand from patients and prescribers to use it as a first line treatment for moderate to severe depression rather than limiting its use to patients who have failed to respond to SSRIs and other antidepressants [161]. It is unclear whether drug regulators will require trials of psilocybin as a first line treatment or whether widescale off label use will prevent any clinical trials from being completed. Psilocybin may also be used off label to treat common anxiety disorders, whose symptoms often overlap with depression and also respond to SSRI antidepressants [157].

12.2 MDMA for PTSD

If MDMA-assisted psychotherapy is approved to treat PTSD, the cost of delivering 15 hours of psychotherapy by two trained therapists will limit access. In the USA, MDMA-AP may be approved by the US Veterans Administration to treat PTSD arising from military service. Patients who have health insurance coverage may also receive subsidised treatment, if the benefits of treatment can be shown to outweigh its costs. The treatment will be less accessible to patients who have limited health insurance coverage.

The cost of the MAPS model of MDMA-AP will no doubt stimulate research into reducing the duration of psychotherapy. This would be sensible because there is weak evidence that longer psychotherapy produces greater benefits at a reasonable cost than shorter therapies. MDMA could, for example, be used with exposure-based forms of psychotherapy, rather than the psychodynamic approach used by Doblin and colleagues. There may also be patient demand to use MDMA off label in the psychotherapeutic treatment of anxiety, depressive disorders and addictions (on the basis that addiction is often the result of a failed attempt to self-medicate anxiety or depression). If the criteria for qualified therapists were liberalised, MDMA could be used to treat unhappiness, milder anxiety disorders and existential angst.

12.3 Early compassionate access to psychedelics

Because results of the early trials of MDMA and psilocybin have been promising, various groups have advocated that patients with PTSD and depression be given early access to psychedelic drugs before pharmaceutical regulators have approved their medical use. This could be done by allowing these drugs to be prescribed as unapproved medicines to individual named patients, as is allowed in many countries. In Australia, for example, Mind Medicine Australia has requested that the pharmaceutical regulator, the Therapeutic Goods Administration, reschedule MDMA and psilocybin to allow their clinical use in this way [169] because there is an urgent need for more effective treatments of depression and PTSD. Analogies have been drawn between demands for early access to psychedelics and the campaign in the 1990s for early access to unapproved treatments for AIDS before the advent of highly effective anti-retroviral drugs [170].

A major risk in providing early compassionate access is that the medical use of psychedelic drugs will follow the trajectory of medical cannabis by getting well ahead of the evidence on their efficacy and safety. For example, as noted above, the evidence in the efficacy for psilocybin in depression could be used by patients and advocates to demand early access to psychedelic drugs for "medical use" to treat conditions in which there is limited evidence on safety and effectiveness, e.g., obsessive compulsive disorder, various types of addiction, autism, and other developmental disorders. There may also be demands for patients to have compassionate access to psychedelic drugs that have not been evaluated for their conditions, such as LSD, mescaline, and DMT.

Allowing compassionate access may reduce incentives for commercial entities to conduct clinical trials of psychedelic drugs [171]. The Australian Federal government has announced substantial funding for clinical trials of psychedelics that will attract new researchers into the field [1,172]. A history of the AIDS epidemic in the United States by a former member of ACT-UP suggests that allowing early access to unapproved drugs for HIV/AIDS delayed clinical trials of effective antiretroviral drugs —the results of which transformed AIDS from a terminal illness into a treatable chronic condition [173].

Experiences in North America, Europe, and Japan with accelerated approvals of "promising" new drugs provides further reasons for caution. These drugs were granted early marketing approval on the condition that the pharmaceutical company sponsor would monitor their safety and effectiveness after their introduction into clinical use. Critics argue that this approach has not delivered earlier access to safer and more effective drugs, as was obvious with the rollout (and later roll-back) of hydroxychloroquine to treat severe acute respiratory syndrome coronavirus infection. More generally, it has been difficult and expensive to assess the clinical value of drugs in the observational studies conducted after their approval. It takes time to identify drugs that are of no benefit and clinical practice may be slow to cease using drugs found to be ineffective, or unsafe, such as the opioids for chronic noncancer pain [174,175].

Allowing compassionate access to pharmaceutical grade psychedelics may create a precedent for allowing compassionate access to plant-based psychedelic drugs where there is an absence of evidence from clinical trials. Some justify the use of these plant-based drugs by appealing to the putative "entourage" effects of whole plants [176] and popular cultural memes that medicines from whole natural plants are safer and more effective than "synthetic" pharmaceuticals.

12.4 Medical psychedelic use via popular referenda

In some US states, advocates of psychedelic use are following the example set by medical cannabis in seeking to pass citizen-initiated referenda that will legalise the medical use of psychedelic mushrooms, peyote, ibogaine and ayahuasca. So far this has happened only in Oregon [112,176,178,179] and in a number of US cities. If this were to happen in more US states, we may see the commercial production and sale of plant-based psychedelic drugs under minimal medical oversight, as happened with medical cannabis. It is uncertain how medical use of psychedelic drugs will affect the right to use micro doses of LSD and other psychedelics for "wellness and creativity" [180].

The popular media have provided very positive coverage of the putative therapeutic benefits of psychedelic drugs. This has changed public perceptions of psychedelic drugs from primarily drugs of abuse to panaceas for the treatment of all mental disorders and the alleviation of major societal problems [2,137]. This has prompted some leading researchers to caution against therapeutic enthusiasm for psychedelics getting ahead of the evidence and premature adoption by poorly trained and supervised therapists producing harms that will endanger support for a promising new treatment (e.g., [149,181]).

13 Nonmedical uses of psychedelic drugs

13.1 Legalisation of psychedelic drugs for religious uses

Some advocates of psychedelic drugs hope that legalisation of their medical use will facilitate the legalisation of adult use [18]. They aim to follow the model of liberal medical cannabis programs in the USA and Canada that facilitated the legalisation of adult cannabis use [182,183,184].

In 1966 Timothy Leary adopted a different tack in arguing for the legalisation of psychedelic drugs for religious purposes by appealing to the freedom to practice one's religion under the US Constitution. He made his case by establishing a League of Spiritual Discovery whose religious practices involved the use of psychedelic drugs [185]. The legalisation of psychedelics for religious purposes has had limited success in the USA since Leary's attempt. In 1994, Congress legislated to allow members of the Native American Church to use peyote in their religious ceremonies. In 2005 the US Supreme Court ruled in favour of the O Centro Espírita Beneficiente União do Vegetal in allowing the use of ayahuasca in religious ceremonies [186]. Some argue that this federal law and Supreme Court case provide precedents for the legalisation of the religious uses of other psychedelic drugs [187].

If the use of psychedelic drugs is permitted for religious purposes, under what conditions should it be allowed? In Congressional testimony in 1966 Timothy Leary proposed that psychedelic centres be licensed so that trained staff would prepare and watch over persons who wanted to be spiritually enlightened by using LSD and other psychedelic drugs [185]. A recent feature published in Nature discussed the possibility that the FDA could use its Risk Evaluation and Mitigation Strategies mechanism to mandate such certification requirements [113].

13.2 Legalisation of adult psychedelic use

Libertarians argue that the state should not interfere in the right of adults to engage in drug use, even when it harms themselves, so long as their drug use does not harm others [188]. Others appeal to the concept or principle that adults have a presumed "cognitive liberty" to use any and all drugs, including psychedelics [189]. A combination of libertarian and utilitarian arguments has also been used to justify the legalisation of adult drug use [190], namely, that adults should be legally permitted to use psychedelic drugs because they cause very little harm to users and they have a low abuse potential [191].

In the USA, activist group Decriminalize Nature, a national organisation with numerous local chapters is campaigning for referenda to legalise the use of plant-based psychedelic drugs such as ayahuasca, ibogaine, peyote, and psilocybe mushrooms, and plants that contain indoleamines, tryptamines, and phenethylamines. The organisation is conducting an "educational campaign to inform individuals about the value of entheogenic plants and fungi" and "to decriminalize our relationship to nature" by legalising the adult use of these drugs [192]. The adult use of psychedelic mushrooms has already been decriminalised by referenda in several US cities including Denver, Colorado [137,193] and there was a proposal for citizen-initiated referenda to allow the adult use of mushrooms in California [194]. Decriminalize Nature's campaign has attracted hostility from members of the Native American Church who see it as a form of cultural appropriation that endangers the supply of the peyote cactus that they use in their ceremonies [195]. A recent paper by an anthropologist and bioethicist has criticised the medicalisation of traditional uses of psychedelic medicines [190].

Similarly, Yaden et al [181] have observed that:

> cultural forces such as those that occurred in the 1960s may threaten contemporary research progress and the clinical application of psychedelics. For example, numerous recent popular press books, websites, podcasts, and media reports have uncritically promoted presumed benefits of psychedelics. Patient demand is growing, as is interest in the general population, with the possibility that expectations are outpacing the current data on what outcomes can be confidently foreseen. Psychedelics are neither a cure for mental disorders nor a quick fix for an unfulfilled life and should not be portrayed as a panacea. Ominously, propsychedelic subcultures are increasingly fostering utopian visions for society based on research findings that, while intriguing, still must be considered preliminary.

14 Conclusions

Psychedelic assisted psychotherapy using psilocybin and MDMA has shown promise in treating depression, post-traumatic stress disorders and addiction in small scale clinical trials. These findings have increased the number of clinical trials now underway and attracted venture capital investment in these therapies. They have also led to a revival of their clinical use and generated pressure from advocates for the clinical use of psychedelic therapies before larger scale trials of safety and effectiveness have been completed. The early history of psychedelic therapies provides strong grounds for the cautious introduction of psychedelic therapies into routine clinical practice if we are to avoid replicating the results of earlier examples of irrational exuberance.

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