Back to the future: Research renewed on the clinical utility of psychedelic drugs

Jeffrey A Lieberman and Daniel Shalev

Two articles in this issue, Ross et al. and Griffiths et al., describe the use of psilocybin in the treatment of depression and anxiety in cancer patients. In doing so, they contribute to a resurgence of interest in research on psychedelic medications that was abruptly banned by the Controlled Substances Act of 1970 because of their popularization and excessive recreational use (Nichols, 2016; Vollenweider and Kometer, 2010). Psilocybin is a plant alkaloid derived from the *Psilocybe* genus of mushrooms that has been used for centuries, if not millennia, by indigenous cultures for ritualized healing and religious purposes. It was scientifically classified as a psychotomimetic (mimicking psychosis) in medical parlance or psychedelic (mind expanding) in the cultural terms of the 1960s, following the discovery of lysergic acid diethylamide (LSD) by a Sandoz (now part of Novartis) chemist in 1943 (Hofmann et al., 1958; Nichols, 2016).

In the 1950s and 1960s, there was robust scientific interest in psychedelic compounds, and they were studied as tools to understand the neurobiology of mental functions and as therapeutic agents for mental disorders, including substance abuse, depression, personality disorders (e.g., antisocial), and palliative care, and as adjuncts to psychotherapy (Nichols, 2016; Unger, 1963). Psychedelics were also studied for more nefarious purposes, such as brainwashing and prisoner interrogation (Johnson et al., 2008).

However, the scientific investigation of this drug class was overshadowed by their widespread recreational use and association with the cultural turmoil and anti-Vietnam War politics of the period. Consequently, following the Controlled Substances legislation of the United States, psilocybin and other psychedelics were classified as schedule I drugs by the United Nations Convention on Psychotropic Substances in 1971 (Nutt et al., 2013). Schedule I substances are considered to have high abuse potential, poor safety, and no therapeutic indication (Rucker, 2015). Criminalization of psychedelic drugs effectively prevented further research into their potential experimental and therapeutic uses for several decades.

Although legal restrictions on psychedelic compounds have been stringent, the evidence that psilocybin causes harm is scant. In a US cohort of 130,152 adults from the National Survey on Drug Use and Health, among whom 21,967 reported lifetime psychedelic use, there was not an increased prevalence of mental illness or suicide in psychedelic use cohorts (Krebs and Johansen, 2013). In fact, lifetime use of psychedelics was associated with increased measures of psychologic well-being (Hendricks et al., 2015). In a review prepared for the Dutch Ministry of Health by a government body tasked with assessment and monitoring of drugs, psilocybin-containing mushrooms were concluded to have minimal potential for harm to either individual or public health and no evidence for dependence or withdrawal (van Amsterdam et al., 2011). Psychologic adverse effects such as anxiety occur, but are time limited. More serious adverse events including self-harm under the influence of psychedelic compounds or prolonged psychotic symptoms are rare, and may be limited to a subset of individuals who are vulnerable to such pathologic reactions (Johnson et al., 2008).

Over the past decade, there has been a resurgence of scientific interest in psychedelic drugs. In this context, the studies reported in this issue add to this renewed interest and growing body of work. Griffiths et al. (2016) found a substantial therapeutic effect of two drug administrations (low and higher doses) in a crossover design on the target symptoms of anxiety and depression in a heterogeneous group of cancer patients with comorbid psychopathology that appeared to be dose related and persisted over the six-month duration of the study. The therapeutic effect was closely tied to the mystical nature of the patients' experiences.

In a similar study, Ross et al. (2016) administered psilocybin or active placebo (niacin) to patients with life-threatening cancer, and assessed effects on anxiety and depression, as well as mystical experience and quality of life. They found a robust therapeutic effect on the target symptoms that was correlated with intensity of mystical experience and persisted for the six-and-a-half-month follow-up period. Both studies had no serious and minimal adverse effects.

These studies reflect the therapeutic promise of psilocybin and related compounds for clinical applications such as cancer-associated psychopathology for which treatments of limited efficacy currently exist. At the same time, they also reveal large gaps in our knowledge that warrant further research in order to exploit fully the value of this novel class of medicinal compounds. The major methodologic limitations of the studies are their crossover

Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital, and New York State Psychiatric Institute, New York, NY, USA

Corresponding author:
Jeffrey A Lieberman, Columbia University, New York State Psychiatric Institute, 1051 Riverside Dr New York, NY 10032, USA.
Email: JLieberman@columbia.edu

designs and the lack of a precisely defined therapeutic dose range. The former is subject to carry-over effects of the experimental treatment, and the latter limits understanding of the true efficacy and safety of the medications, as well as their duration of action and optimal frequency of administration. Moreover, we do not know how the setting or mode of administration influences treatment effects and outcome.

A greater concern is the lack of understanding of the mechanism of action of psychedelic drugs. While we know that they are agonists at 5-HT-2A receptors (Nichols, 2016), which is believed to produce subjective effects of perceptual disturbances, sensations of spiritual oneness or mystical ecstasy, and, at times, paranoia or anxiety (Vollenweider and Kometer, 2010), the mechanism mediating such effects is incompletely understood. It is thought that 5-HT-2A receptor agonism may stimulate beta arrestin intracellular signaling pathways and modulate prefrontal cortical pyramidal neurons affecting neuroplastic adaptations. Psychedelic compounds have been demonstrated to modulate amygdala reactivity to neutral and negative stimuli, also through 5-HT-2A receptor agonism (Kraehenmann et al., 2015; Nichols, 2016). Yet, this tells us little about how they induce an altered state of consciousness with spiritual qualities. In addition, we cannot tell if the anxiolytic and antidepressant effects of the drugs are direct results of their serotonergic effects or secondary to the mystical altered state of consciousness that they produce. Since other serotonin agonists (e.g., lisuride) do not produce this psychedelic experience, it has been suggested that psychedelic drugs must bind to the 5-HT2A receptors in a special way, or exhibit functional selectivity or receptor bias (González-Maeso et al., 2008).

While the use of psychedelic compounds without a complete mechanistic understanding is concerning, it is not unique. The therapeutic mechanisms of other nearly-miraculous drugs such as aspirin and clozapine remain mysterious. In a similar vein, ketamine, which is increasingly used to treat severe depression, with the potential for expanded utility for other conditions, is also poorly understood in terms of mechanism, frequency of administration, and dosing (Newport et al., 2015).

The reemergence of psychedelic drugs from a controversial past and an interruption in their development is also not unique. Other breakthrough drugs such as clozapine and thalidomide have had their initially promising development abruptly halted for reasons of toxicity before being revived successfully. Clozapine's initial development was interrupted by a series of fatalities caused by drug-induced agranulocytosis (Alvir et al., 1993) before being resumed a decade later after its superior efficacy in treatment-resistant patients was appreciated (Kane et al., 1988). Thalidomide was initially used to treat morning sickness in pregnant women, but withdrawn from the market in 1961 due to teratogenic effects in newborns (Vargesson, 2015). In 1998, it was approved by the Food and Drug Administration for the treatment of leprosy and subsequently multiple myeloma (Franks et al., 2004; Gao et al., 2016). It is notable that upon their reintroduction, both drugs were marketed under strictly controlled conditions.

With its renewed interest, psilocybin joins a number of restricted and criminalized compounds as a new focus for psychiatric research. Other such compounds include 3,4-methylenedioxymethamphetamine (MDMA) and tetrahydrocannabinol (THC). These compounds have also had political and legal factors limit their scientific investigation and clinical use.

Renewed interest in the biomedical utility of restricted compounds raises a number of ethical and legal questions. Most centrally, what are responsible ways to utilize such compounds? The dangers of addiction and substance use are acutely clear to the psychiatric researchers most invested in studying such compounds. Still, while compounds such as MDMA, THC, and psychedelics remain unavailable for medicinal use, cannabis products are being increasingly legalized (Hall and Lynskey, 2016), and other compounds with abuse potential, are used therapeutically, namely opiates (Nutt et al., 2013). Such determinations are based primarily on historical contexts; those medications whose medicinal uses were established prior to their abuse potential tend to enjoy ongoing acceptance, while drugs initially associated with abuse are more strictly controlled (Nutt et al., 2013).

While the restriction of compounds with abuse potential is deployed in the interest of public health, much of the policy is not scientifically informed. Many compounds have been criminalized and effectively excluded from research without an understanding of their pharmacology and toxicology (Nutt et al., 2013). Recent studies have demonstrated that the degree of restriction for illegal drugs does not correlate with their risk of harm, and there is no formalized process for reviewing these determinations at the national or international level (Nutt et al., 2010, 2013). Current laws, not based on evidence, impede research by onerous storage and security requirements, difficulty in obtaining funding, and the near impossibility of actually obtaining restricted compounds without having them synthetically produced at great cost (Nutt et al., 2013).

The overwhelming morbidity and mortality of treatment-refractory psychiatric conditions, ranging from mood disorders to addiction, suggest an ethical and public health imperative to use every avenue possible to pursue novel therapeutic agents. We do our patients a disservice by not understanding and appropriately investigating compounds with potential therapeutic value because of their prior controversial associations and on their capacity for misuse. More flexibility in research on such compounds and a more scientifically rigorous basis for classifying and restricting drugs based on their potential physical, social, and psychiatric harms may pave the road for delineation of novel therapeutic and mechanistic data from previously unavailable compounds (Nutt et al., 2010). The work presented in this issue by Griffiths et al. and Ross et al., beyond its obvious implications for patients with comorbid advanced cancer and depression and anxiety, serves as a model for revisiting criminalized compounds of interest in a safe, ethical way. Should more members of the biomedical community follow their lead, there is much potential for new scientific insights and clinical applications.

Declaration of conflicting interests

Funding

References

Alvir JM, Lieberman JA, Safferman AZ, et al. (1993) Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *New Engl J Med* 329: 162–167.

Franks ME, Macpherson GR and Figg WD (2004) Thalidomide. *Lancet* 363: 1802–1811.

Gao M, Kong Y, Wang H, et al. (2016) Thalidomide treatment for patients with previously untreated multiple myeloma: a meta-analysis of randomized controlled trials. *Tumour Biol* 37: 11081–11098.

González-Maeso J, Ang RL, Yuen T, et al. (2008) Identification of a serotonin/glutamate receptor complex implicated in psychosis. *Nature* 452: 93–97.

Griffiths RR, Johnson MW, Carducci MA, et al. (2016) Psilocybin produces substantial and sustained decrease in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol*.

Hall W and Lynskey M (2016) Why it is probably too soon to assess the public health effects of legalisation of recreational cannabis use in the USA. *Lancet Psychiatry* 3: 900–906.

Hendricks PS, Thorne CB, Clark CB, et al. (2015) Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *J Psychopharmacol* 29: 280–288.

Hofmann A, Heim R, Brack A, et al. (1958) [Psilocybin, a psychotropic substance from the Mexican mushroom Psilicybe mexicana Heim]. *Experientia* 14: 107–109.

Johnson M, Richards W and Griffiths R (2008) Human hallucinogen research: guidelines for safety. *J Psychopharmacol* 22: 603–620.

Kane J, Honigfeld G, Singer J, et al. (1988) Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 45: 789–796.

Kraehenmann R, Preller KH, Scheidegger M, et al. (2015) Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. *Biol Psychiatry* 78: 572–581.

Krebs TS and Johansen P-Ø (2013) Psychedelics and mental health: a population study. *PLOS ONE* 8: e63972.

Newport DJ, Carpenter LL, McDonald WM, et al. (2015) Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry* 172: 950–966.

Nichols DE (2016) Psychedelics. *Pharmacol Rev* 68: 264–355.

Nutt DJ, King LA, Phillips LD, et al. (2010) Drug harms in the UK: a multicriteria decision analysis. *Lancet* 376: 1558–1565.

Nutt DJ, King LA and Nichols DE (2013) Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nat Rev Neurosci* 14: 577–585.

Ross S, Bossis A, Guss J, et al. (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol*.

Rucker JJH (2015) Psychedelic drugs should be legally reclassified so that researchers can investigate their therapeutic potential. *BMJ* 350: h2902.

Unger SM (1963) Mescaline, LSD, psilocybin, and personality change. *Psychiatry* 26: 111–125.

van Amsterdam J, Opperhuizen A and van den Brink W (2011) Harm potential of magic mushroom use: a review. *Regul Toxicol Pharmacol* 59: 423–429.

Vargesson N (2015) Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res C Embryo Today* 105: 140–156.

Vollenweider FX and Kometer M (2010) The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. *Nat Rev Neurosci* 11: 642–651.