

## EDITORIAL

# Psychiatry might need some psychedelic therapy

In historical and modern-day studies, psychedelic drugs have shown promise in managing a variety of psychiatric disorders, but their medical use has often raised controversies. The controversies have related to social, political, and legal challenges.

## History

Although anthropological evidence suggests that classic psychedelic drugs (hereafter, 'psychedelics') have been used by various indigenous peoples as sacraments and healing agents before recorded history, in the mid-twentieth century they came to occupy a place at the cutting edge of psychiatric research (Johnson, Richards, & Griffiths, 2008). Although some psychiatrists and researchers might be under the impression that this interest was a fad, this is far from the case. Over 1000 papers were published describing the treatment of over 40,000 patients with psychedelics (Grinspoon, 1981). The discovery of lysergic acid diethylamide (LSD), with its extremely powerful subjective effects caused by infinitesimal doses, and with its structural similarity to the newly-discovered neurotransmitter serotonin, was a strong contributor to the emerging neuroscientific model that took hold in the 1950s and 1960s. In large part this new biobehavioural understanding of brain function came to replace psychodynamic models as the predominant paradigm in psychiatry.

In addition to the role of psychedelics as tools for investigating the biological substrates of the mind and behaviour (considered two sides of the same coin by the present author), promising therapeutic applications were investigated, with particularly promising findings in the treatment of both addiction and cancer-related psychiatric existential distress (Johnson & Griffiths, 2017). However, despite initial excitement, research on these drugs became increasingly marginalized due to their growing use outside of clinical research settings, and their resulting association with the counter-culture movement in the late 1960s and early 1970s. These compounds are powerful tools. Like all powerful tools, use by the incautious and unwise can (and did) lead to demonstrable harms (Carbonaro et al., 2016; Johnson et al., 2008).

Although a few investigators who abandoned a scientific approach became 'poster children' for why these tools could not be trusted to scientists for human research, psychiatric pioneers such as Humphrey Osmond, Abram Hoffer, Walter Pahnke, and Sidney

Cohen, who are scientific heroes to the present author, were more representative of the many scientists who conducted ethical and responsible human research with psychedelics, and who knew that addressing the very real risks of these compounds was essential to making scientific and therapeutic progress. Unfortunately for investigators like these, and for patients who might have benefitted from the fruits of cautious human psychedelic research decades ago, the early promising scientific threads of psychedelic research remained dangling for decades (Tupper, Wood, Yensen, & Johnson, 2015).

## Re-emergence

In the 1990s a small number of investigators in Europe and the US re-initiated human studies with psychedelics. Non-human research in the intervening decades had identified agonist activity at the 5-HT<sub>2A</sub> receptor as a key mechanism underlying the effects of psychedelics (e.g. Glennon, Titeler, & McKenney, 1984), which include LSD as well as psilocybin (present in many species of mushrooms), mescaline (present in peyote and other cacti), and dimethyltryptamine (DMT; present in a wide variety of plants). Studies by researchers in the modern era have followed established safety guidelines for administering psychedelics (Johnson et al., 2008). Like the best of the original era of research, these guidelines involve careful screening and preparation before drug administration sessions, intense monitoring during sessions, and follow-up care involving both clinically supportive discussion of session experiences and assessment for any adverse effects resulting from the session. Moreover, modern investigators have often approached this research using methods and technologies that were non-existent or not fully established in the earlier era of research, including psychometrically validated scales, double-blind and even more complex designs, and brain imaging. These early studies led to more studies at a growing number of prominent universities as the safety and potential efficacy of clinical psychedelic research was demonstrated. Therapeutic studies using psychedelics have been reported for depression and anxiety related to cancer and other life-threatening illness (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), treatment-resistant depression (Carhart-Harris et al., 2016; Palhano-Fontes et al., 2018), tobacco addiction (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Johnson, Garcia-Romeu, & Griffiths, 2017), and alcohol addiction (Bogenschutz et al., 2015).

Some studies have been randomized trials, while others have been initial open-label pilot trials designed to establish safety in new populations and test the waters for future randomized trials. Remarkably, some of these studies have reported rapid efficacy persisting for at least 6 months after one or a few administrations. In comparison, ketamine, which is under investigation for depression treatment and has greater addiction potential than psychedelics (Johnson, Griffiths, Hendricks, & Henningfield, 2018; Kolar, 2018), has been considered rightly a potential breakthrough for showing immediate antidepressant effects that persist for about a week after administration (Molero et al., 2018). Therefore, psychedelics might be considered to have even greater breakthrough potential.

Consistent with these laboratory studies, a growing number of epidemiological studies have found suggestive associations between naturalistic use of psychedelics and positive outcomes using regression models controlling for other variables including use of other drugs. For example, one study, based on a nationally representative survey of over 190,000 individuals, found that lifetime classic psychedelic use (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015), including psilocybin use (Hendricks, Johnson, & Griffiths, 2015), was associated with reduced psychological distress and suicidality in the US adult population. Potentially suggestive of anti-addiction effects, another study, based on over 25,000 individuals, suggested that psychedelic use (broadly defined) was associated with reduced recidivism from drug-related and other criminal activity among drug-involved criminal offenders undergoing community supervision (Hendricks, Clark, Johnson, Fontaine, & Cropsey, 2014).

### Psychiatry needs help

Psychiatry, and society itself, finds itself faced with greater challenges than ever before. The US, home of the present author, is facing epidemic rates of suicide (Stone et al., 2018) and opioid addiction fatalities (Kolodny et al., 2015). Tobacco addiction remains a staggering killer, with about a half million people in the US (U.S. Department of Health & Human Services, 2014), and about six million people, globally, dying from tobacco related disease annually (World Health Organization, 2011). Bucking a decades-long trend in the opposite direction, between 1999 and 2013, mortality among middle-aged white, non-Hispanic adults in the US (i.e. a relatively advantaged demographic) showed a marked increase, primarily due to substance use and suicide (Case & Deaton, 2015). These are behaviourally mediated problems—the turf of psychiatry.

The last major advance in the treatment of depression was ~30 years ago with the clinical approval of the first selective serotonin reuptake inhibitors. Even these were simply more selective and safer compounds capitalizing

on general mechanisms at play for older generations of antidepressants developed in the 1950s. Make no mistake, these are critical tools in the therapeutic toolbox that have helped many people. Meta-analysis suggest that effect sizes are relatively modest (e.g. Cipriani et al., 2018), but even small effect sizes for depression can be of critical help for those whose depression puts them at risk for suicide. However, there is a clear need for, and substantial room for, improvement. The state of addiction medicine is likewise disappointing. For many, but not all substances of addiction, approved medications are available that perform better than placebo. Even with these important medications, relapse rates are substantial and in dire need of improvement (McLellan, Lewis, O'Brien, & Kleber, 2000).

Aside from the need for more effective treatment options, psychiatry is in desperate need of fundamental mechanistic advances. Several years ago, the US National Institute of Mental Health (NIMH) made the decision to no longer fund research that only uses the Diagnostic and Statistical Manual of Mental Disorders (DSM) to describe psychiatric illness, due to the framework's relative lack of scientific rigour. Unlike other areas of medicine, psychiatry relies on a largely superficially descriptive, rather than mechanistic, understanding of its various disorders. Surely, this relative dearth of a mechanistic understanding of the various disorders must be related to psychiatry's slow and modest advances in treatments, and resulting unmet clinical needs.

The present author holds that psychedelics may be poised to make fundamental advances in a mechanistic (both biological and psychological) understanding of psychiatric disorders. It should be curious, and indeed, raise suspicions of 'snake oil,' that psychedelics are showing promise for supposedly distinct and wide-ranging psychiatric disorders, including depression and anxiety, and addictions across a variety of drugs. However, an emerging biological narrative might be unfolding, related to the ability of these drugs to acutely increase global brain network synchronization, and to disintegrate default mode network activity, a biological pattern of connectivity that may underlie the sense of self (Carhart-Harris et al., 2012, 2017). If continued research shows psychedelic therapy to cause lasting changes in default mode network and other brain network activity across multiple disorders, then the common biobehavioural mechanism at play may rest in the long-term adjustment of rigid, sub-optimal brain network activity associated with the narrowed behavioural and mental repertoires common to all of these disorders (Nichols, Johnson, & Nichols, 2017). Whether it is the self-persecutory thoughts and decreased activity in those with depression, the apprehensive thoughts and preventative behaviours in those with anxiety disorders, or the high rates of drug self-administration to the exclusion of other priorities (and accompanying hopeless thoughts) with substance use disorders, these might all be

conceptualized as addiction, broadly defined. Other commonalities, for example, potential inflammation effects common across some psychiatric disorders which might be addressed by potential long-term anti-inflammatory effects of psychedelics, discussed by Flanagan and Nichols in this issue, might also emerge. Therefore, not only might psychedelics provide robust efficacy across multiple disorders, they might also constitute breakthrough tools in taking psychiatry to the next level in terms of understanding mechanistic commonalities across supposedly distinct disorders.

Importantly, the mechanisms underlying psychedelic efficacy might be both biological *and* psychological. For decades, non-empirically-grounded terms such ‘ego death’ have been used to describe the acute effects of these drugs. As discussed above, research now suggests a very real, empirically supported biology may underlie such effects. Moreover, patients in research trials commonly report narrative, psychological content at play when psychedelic therapy appears successful, such as achieving a fundamental, molar understanding of themselves, their connections to others, and insights into the issues from which they suffer (e.g. Noorani, Garcia-Romeu, Swift, Griffiths, & Johnson, 2018). Indeed, it seems that, unlike with most psychiatric medications, patients are doing their own psychological ‘heavy lifting’ when they receive psychedelic therapy, perhaps affording a greater sense of agency compared to other psychiatric medications. In this respect, the return of psychedelics to psychiatry might constitute a return of psychiatry to its roots, before the focus on biology and the brain took center stage, with a psychological understanding focused on the sense of self as it interfaces with personal history and the environment, as in the psychodynamic models which once predominated. However, this homecoming now involves a more empirically grounded approach bridging both psychology and neuroscience—the best of both worlds.

### Whatchu talkin’ ‘bout, Willis? These are drugs of abuse!

An understandable initial reaction by many psychiatrists and researchers may be skepticism. Especially for those on the clinical front lines, the implicit association with psychedelics is negative. As they are controlled substances, their use is often associated with the use of other illicit substances. Also their use, particularly in uncontrolled contexts, can lead to anxiety reactions and resultant dangerous behaviour. For those with psychotic disorders or predisposed to these disorders, psychedelic use may lead to prolonged adverse reactions and harm to mental health. However, a critical distinction is that, while these factors lead to psychedelics being considered drugs of abuse or misuse when used in an uncontrolled setting, it is well established that psychedelics are not

drugs of addiction or compulsive drug seeking. Moreover, modern safety guidelines squarely address these concerns to minimize such risks in clinical research, affording a radically different safety profile compared to uncontrolled psychedelic use (Carbonaro et al., 2016; Johnson et al., 2008, 2018).

If it seems strange that a class of abused drugs is being developed for therapeutic potential, consider that psychedelics are actually the only major class of abused drugs that do *not* already have therapeutic uses recognized by regulatory bodies such as the US Food and Drug Administration (FDA). While medicine is currently trying to find a balance between their use and risks, opioids are indispensable to medicine as analgesics, despite being associated with high addiction potential and acute fatal overdose. Methamphetamine, amphetamine, and similar stimulants with very high addiction potential are approved for the treatment of attention deficit disorder. Cocaine is approved for topical use as an anaesthetic in otolaryngologic procedures. Benzodiazepines, barbiturates, and mechanistically related GABAergic sedatives are often abused but approved as anxiolytics and hypnotics. Finally, despite the controversy and current mixed state-federal legal status of plant cannabis in the US, there is no controversy whatsoever about the clinical use of dronabinol (tetrahydrocannabinol or THC), which was FDA approved over 30 years ago, and is used to treat chemotherapy-related nausea and vomiting, as well as appetite and weight loss in HIV patients (Because clinical development is occurring for synthetic psilocybin, rather than psilocybin-containing mushrooms, the appropriate analogy would indeed be to dronabinol rather than plant cannabis.). Drawing from these trends, it would almost be surprising if psychedelics did *not* have therapeutic potential, at least in limited circumstances, especially given their substantially lower physical toxicity and addiction potential in comparison to the other psychoactive drugs with approved therapeutic use (Johnson et al., 2018).

### Why now?

Despite two decades of dormancy (mid-1970s to mid-1990s), and two decades in which professional acceptance for the few scientists involved was questionable, and the prospect of governmental funding of therapeutic studies seemed a pipe dream (mid 1990s–recently), mainstream scientific and societal acceptance of human psychedelic research seems it might be finally taking off. Perhaps the best current example is the recent publication of acclaimed author Michael Pollan’s book *How to Change Your Mind: What the New Science of Psychedelics Teaches Us About Consciousness, Dying, Addiction, Depression, and Transcendence* (Pollan, 2018), currently on the *New York Times* Best Seller list. Pollan, best known for his non-fiction books on food and

agriculture, spent years delving into scientific laboratories around the world in order to render the modern era of psychedelic research digestible to Jane and John Q. Public. Whether his synthesis substantially moves the needle regarding scientific and public support for psychedelic research remains to be seen, but book sales and his high-profile interviews promoting the book would suggest it has at least piqued some substantial curiosity.

Why did it take decades for such research to reinstate and gain hold? There were surely many factors at play at different levels of analysis, but perhaps at the molar behavioural level, time simply had to move forward, consistent with Thomas Kuhn's description of the unfolding of scientific revolutions or new paradigms (Kuhn, 1962). Kuhn cites physicist Max Planck, founder of quantum theory, in making the point: '[A] new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it' (Planck, 1949, p. 33–34).

Kuhn (1962) reminds us that Isaac Newton's *Principia* (Newton, 1687), one of the greatest scientific works in history, was not met with general acceptance for more than 50 years after its publication. Kuhn also cites Charles Darwin, whose wisdom allowed him to accurately predict a similar fate for *On the Origin of Species*, also among humanity's greatest scientific works. As Darwin (1859) wrote in the conclusion of that hallowed scientific volume:

Although I am fully convinced of the truth of the views given in this volume under the form of an abstract, I by no means expect to convince experienced naturalists whose minds are stocked with a multitude of facts all viewed, during a long course of years, from a point of view directly opposite to mine ... A few naturalists, endowed with much flexibility of mind, and who have already begun to doubt the immutability of species, may be influenced by this volume; but I look with confidence to the future, to young and rising naturalists, who will be able to view both sides of the question with impartiality (p. 481–482).

When it took generations to pass for the seminal works of Isaac Newton and Charles Darwin to take hold in humanity's collective scientific understanding, psychedelic researchers find themselves in some respectable company, to say the least. So, although those advancing the scientific and therapeutic potential of psychedelics might understandably feel frustrated at the opportunities lost, perhaps this history was to be expected.

### Current issue and new directions in psychedelic research

The current issue of *International Review of Psychiatry* contains a number of exciting manuscripts focused on the scientific potential and clinical use of psychedelics,

written by leading experts with backgrounds in psychiatry, psychology, neuroscience, and pharmacology. Although the focus is on the classic 5-HT<sub>2A</sub> agonist psychedelics, related compounds with differing but somewhat overlapping mechanisms, such as methylenedioxymethamphetamine (MDMA), are occasionally addressed. As clinical research interest in psychedelics is rapidly increasing, special attention has been paid to curate both summaries of the current landscape of clinical psychedelic research, as well as previously unexplored topics, including both psychological and biological mechanisms, and novel potential future therapeutic modalities and theoretical frameworks for understanding psychedelic therapy.

Psychologists Albert Garcia-Romeu, PhD, and William Richards, PhD, provide an overall view of the clinical field of psychedelic research, with a summary of past and present models for conducting therapy with psychedelics, as well as considerations for future interventions. These authors draw from recent specialization in the use of psychedelics in the treatment of addiction from Dr Garcia-Romeu, as well as from several decades of clinical experience from Dr Richards (see Richards, 2015), who is considered a living legend among psychedelic researchers, and who is perhaps the only clinical researcher whose experimental research spans both the earlier era and current eras of human psychedelic research.

Stephen Ross, MD, is an addiction psychiatrist who also has expertise in the treatment of cancer-related existential distress. Dr Ross and colleagues conducted one of the recent, large randomized, double-blind, clinical trials showing substantial and sustained anti-depressant and anxiolytic effects of psilocybin in cancer patients. Dr Ross provides a broad review of the literature on existential distress associated with cancer. He then reviews research from both the previous and modern eras of research, showing promising effects of psychedelics for this indication.

Peter Hendricks, PhD, is a clinical psychologist who is currently conducting a randomized, double-blind study examining the therapeutic potential of psilocybin in the treatment of cocaine addiction, a trial for which he recently presented promising preliminary results for psilocybin-occasioned cocaine abstinence at the 2018 meeting of the *College on Problems of Drug Dependence*. In his manuscript in this issue, Dr Hendricks provides a fascinating psychological theory of psychedelic therapy, embedding psychedelic-occasioned mystical-type experiences within the literature surrounding the psychological construct of awe. Awe refers to an experience in which a stimulus is encountered that is so vast that it prompts a modification in the sense of self, resulting in a 'small self' with therapeutic import.

Zach Walsh, PhD, a clinical psychologist in Canada with expertise in applying 'third wave' behaviour therapies to addressing intimate relationship conflict and

substance use disorders, along with Michelle Thiessen, provide a review which explores the possibility of applying third wave behaviour therapies to enhance psychedelic therapy. Third wave behavioural therapies go beyond Cognitive Behaviour Therapy (the ‘second wave’) to include a number of relevant constructs, such as mindfulness, to provide a sophisticated understanding of behaviour change. Such therapies include empirically supported approaches such as Dialectical Behaviour Therapy, Acceptance and Commitment Therapy, and Mindfulness Based Cognitive Therapy. After identifying implicit commonalities between third wave behavioural approaches and psychedelic therapy, these authors go on to make recommendations for the explicit integration of third wave approaches to enhance psychedelic therapy in the treatment of psychiatric disorders.

Frederick Barrett, PhD, Katrin Preller, PhD, and Mendel Kaelen, PhD, an international team of neuroscientists and psychologists with expertise in affective neuroscience and music, provide a review of the history and recent research showing the critical role of music in psychedelic therapy sessions. Moreover, they explore psychological and biological mechanisms by which psychedelics may be used as tools to understand the mechanisms for the perception of music and the mechanisms underlying profound emotional experiences in general. Even if some readers cannot follow all of the nuanced notes of their exploration, those readers are sure to be able to follow the music of this fascinating review.

Finally, pharmacologists Thomas Flanagan, PhD, and Charles Nichols, PhD, provide a review of psychedelics as anti-inflammatory agents. After reviewing the role of the 5-HT<sub>2a</sub> receptor in anti-inflammatory response, Dr Flanagan and Dr Nichols review exciting evidence from Dr Nichol’s pharmacology laboratory showing that 5-HT<sub>2a</sub> receptor activation causes potent anti-inflammatory effects in non-human models at very low, sub-behavioural doses, and discuss the potential of psychedelics as a new medication class to treat inflammatory disorders. Further, they discuss the potential that such anti-inflammatory effects might in fact play a role in the persisting therapeutic effects of psychedelics for psychiatric disorders.

This issue of *International Review of Psychiatry* provides both an informative introduction to the uninitiated, as well as a more thorough exploration of psychedelic research for those who have followed this field for years, and perhaps decades! The reader is requested to explore the empirical support for the research described herein. Further, it is hoped that this issue will serve to invite both the skeptical and the enthusiastic (and ideally, those who are both) to conduct their own empirical research in this rapidly growing field. Welcome to the renaissance in psychedelic research!

## Disclosure statement

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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