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Circumspective

The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future

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Plant-based psychedelics, such as psilocybin, have an ancient history of medicinal use. After the first English language report on LSD in 1950, psychedelics enjoyed a short-lived relationship with psychology and psychiatry. Used most notably as aids to psychotherapy for the treatment of mood disorders and alcohol dependence, drugs such as LSD showed initial therapeutic promise before prohibitive legislature in the mid-1960s effectively ended all major psychedelic research programs. Since the early 1990s, there has been a steady revival of human psychedelic research: last year saw reports on the first modern brain imaging study with LSD and three separate clinical trials of psilocybin for depressive symptoms. In this circumspective piece, RLC-H and GMG share their opinions on the promises and pitfalls of renewed psychedelic research, with a focus on the development of psilocybin as a treatment for depression.
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THE THERAPEUTIC POTENTIAL OF PSYCHEDELIC DRUGS: TEMPERED OPTIMISM (RLC-H)

> *"Your assumptions are your windows on the world. Scrub them off every once in a while, or the light won't come in."* (Isaac Asimov, 1919–1992)

A BRIEF HISTORY OF PSYCHEDELIC RESEARCH

Psychedelic drugs (*Psychedelic* is a neologism that combines the words psychē (ψ υ χ ή, 'soul') and dēloun (δ η λ ο ῦ ν, 'to make visible, to reveal'), to denote 'mind-revealing' in reference to the category of drugs in question. I use the term in preference to 'hallucinogens' due to the latter's arguably misleading emphasis on these compounds' hallucinogenic properties. When using the term 'psychedelics' I refer to those compounds with appreciable serotonin 2A receptor agonist properties that can alter consciousness in a marked and novel way. LSD can be considered the prototypical or 'reference-standard' psychedelic.) awakened a significant cultural zeitgeist in mid-twentieth century (Stevens, 1987, see Table 1). Catalyzed by early reports on the unique potency and remarkable subjective effects of lysergic acid diethylamide (LSD) in the early 1950s, psychedelics, and particularly LSD, became widely used by psychologists and psychiatrists in research and clinical practice, with tens of thousands of patients estimated to have been treated with 'psychedelic psychotherapy' over a period of about 15 years (Grinspoon and Bakalar, 1979). From the mid-60s, psychedelic research was increasingly prevented from having the capacity to inform and potentially advance thinking and practice in psychology and psychiatry, but as popular and countercultural movements increasingly embraced the drugs, their societal impact skyrocketed (Grinspoon and Bakalar, 1979; Lee and Shlain, 1992; Stevens, 1987).

THE PRESENT REVIVAL

Human psychedelic research fell into a 25-year hiatus before scientists in Germany (Hermle *et al*, 1992), the United States (Strassman and Qualls, 1994), and Switzerland (Vollenweider *et al*, 1997) began its revival. There now exists a foundation of human neuroimaging (Carhart-Harris *et al*, 2012a, 2016d; Daumann *et al*, 2010; Muthukumaraswamy *et al*, 2013; Palhano-Fontes *et al*, 2015; Preller *et al*, 2017; Riba *et al*, 2004, 2006; Vollenweider *et al*, 1997), psychology (Carhart-Harris *et al*, 2015, 2016c; Carter *et al*, 2007; Gouzoulis-Mayfrank *et al*, 2005; Griffiths *et al*, 2006; MacLean *et al*, 2011; Schmid *et al*, 2015), and psychopharmacology studies with psychedelics (Kometer *et al*, 2012; Preller *et al*, 2017; Valle *et al*, 2016; Vollenweider *et al*, 1998).

These foundational studies complement a small number of early phase clinical trials (Table 2). There are now positive preliminary reports on the safety and tolerability of psilocybin for obsessive compulsive disorder (Moreno *et al*, 2006), psilocybin, and LSD for end-of-life psychological distress (Gasser *et al*, 2014; Griffiths *et al*, 2016; Grob *et al*, 2011;

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Table 1 Notable Landmarks of Mid-Twentieth Century Psychedelic Research Plus Events of Cultural Significance

Year	Landmark	References
1943	LSD's psychoactive effects discovered by Albert Hofmann (16th and 19th April)	Hofmann, 1980
1947	Werner Stoll publishes first paper on psychological effects of LSD in humans	Stoll, 1947
1950	First English language publication on LSD	Busch and Johnson, 1950
c. 1953	ACNP Founding president Joel Elkes (President in 1961) publishes on LSD after openly self-experimenting with it	Bradley *et al*, 1953; Roberts, 2008
1954	Aldous Huxley's 'The Doors of Perception' published: documents mescaline self-experiment	Huxley, 1954
1956	Term 'psychedelic' coined by Humphrey Osmond in communication with Aldous Huxley	Huxley, 1980
1957	Term 'magic mushrooms' coined by LIFE magazine	Wasson, 1957
1958	Identification of psilocybin in magic mushrooms by Albert Hofmann	Hofmann *et al*, 1958
1959	Closed conference held in Princeton on 'the use of LSD in psychotherapy', Jonathan Cole attends, an early ACNP president	Abramson, 1959
1960	First major European conference on psychedelics; Sidney Cohen publishes positive meta-analysis on LSD safety	Passie, 1996; Cohen, 1960
1961	Jonathan Cole (ACNP president 1965-66) expresses 'very mixed feelings on psychedelic research' as critical commentaries emerge	Mangini, 1998
1962	The Marsh Chapel or 'Good Friday' experiment conducted at Harvard under Timothy Leary's supervision but without institutional approval	Pahnke, 1966; Mangini, 1998
1963	Leary dismissed from Harvard; Aldous Huxley and JFK die (both on 22nd November)	Stevens, 1987
1964	Cole takes 'sober look' at psychedelics in JAMA; discussions on LSD take center stage at 1964 APA meeting; Ken Kesey travels across US taking LSD with 'Merry Pranksters'	Mangini, 1998; Cole and Katz, 1964; Stevens, 1987; Wolfe, 1968
1965	Sandoz stop manufacture of LSD and psilocybin	Stevens, 1987
1966	Prohibition of psychedelics and curtailment of research begins in US; Senator Robert Kennedy formally questions this move	Stevens, 1987; Lee and Shlain, 1992
1967	Timothy Leary declares 'turn on, tune in and drop out' at festival in Golden Gate Park	Stevens, 1987
1970	President Nixon signs Controlled Substances Act, LSD and psilocybin made Schedule I	Stevens, 1987; Lee and Shlain, 1992

Abbreviations: ACNP, American College of Neuropsychopharmacology; JAMA, *Journal of the American Medical Association*; NIMH, National Institute of Mental Health.

Ross *et al*, 2016), psilocybin for alcohol (Bogenschutz *et al*, 2015), and tobacco addiction (Johnson *et al*, 2014) and ayahuasca (Osorio Fde *et al*, 2015) and psilocybin for major depressive disorder (Carhart-Harris *et al*, 2016a,b). An important caveat here, is that many of these trials report on small sample sizes and would best be described as 'safety and tolerability' studies by conventional standards (Schunemann *et al*, 2006), and while all of them do report outcomes consistent with potential efficacy, most have not been appropriately designed to demonstrate it conclusively. GMG critically discusses two of the largest and better designed trials in the next section (Griffiths *et al*, 2016; Ross *et al*, 2016).

PSYCHEDELICS FOR MENTAL ILLNESS

Plant-based psychedelics have been used for hundreds if not thousands of years for holistic healing (Hofmann, 1980) and there remains an active culture of self-medication with psychedelics for mental health (Carhart-Harris and Nutt, 2010; Waldman, 2017). Contrary to the alarmist campaigning that so negatively affected perceptions of psychedelics after the 1960s, subjective (Carhart-Harris and Nutt, 2010, 2013; van Amsterdam *et al*, 2015), naturalistic/observational (Bouso *et al*, 2012), and population-based data (Hendricks *et al*, 2015) indicate a positive association between psychedelic drug use and mental health, albeit with some important caveats, which will be discussed below.

Progressing to more controlled medical use, psychedelics piqued the interest of psychologists and psychiatrists in the 1950s, who noted early on that they may 'serve as new tools for shortening psychotherapy' (Busch and Johnson, 1950). A recent meta-analysis of 19 studies of psychedelics for mood disorders published between 1949 and 1973 found that 79% of patients showed 'clinically judged improvement' post treatment (Rucker *et al*, 2016). Moreover, a meta-analysis of studies of LSD for alcoholism performed in the 50–60s was similarly supportive of its potential (Krebs and Johansen, 2012). The absence of standardized diagnostic techniques, measures of symptom severity, and lack of randomization and control conditions in these studies needs to be properly heeded, but equally, it would be self-defeating to dismiss their findings outright.

The modern era of controlled research with psychedelics has seen the adoption of more careful experimental designs, together with a more critical approach to outcomes. In 2006, a double-blind randomized controlled (DB-RC) study compared the acute and longer-term psychological effects of single high doses of psilocybin (30 mg) and methylphenidate (40 mg) in healthy volunteers. Significantly, greater improvements in psychological well-being were observed after psilocybin than methylphenidate at the 2-month end point and more than half considered their psilocybin experience to be among the most personally meaningful experiences of their lives (Griffiths *et al*, 2006). Since then, the focus has shifted to include patients with symptoms of

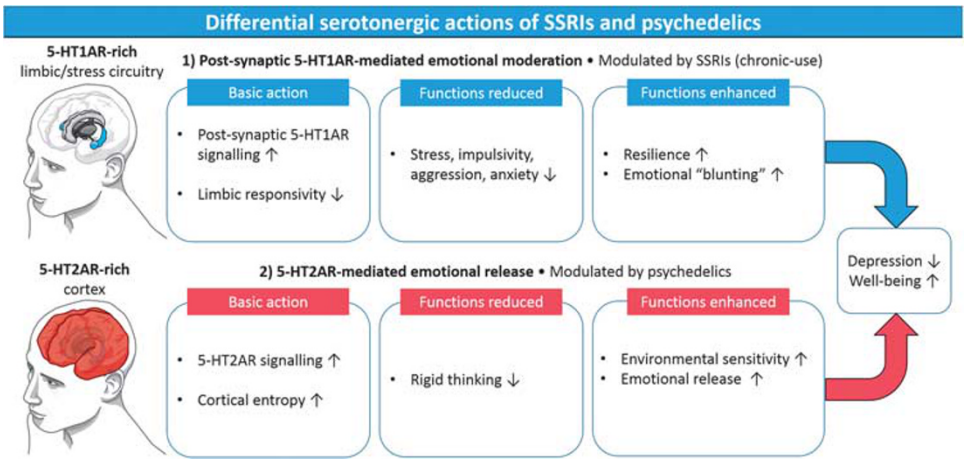

Figure 1 A bipartite model of serotonergic functioning focused on the effects of post-synaptic 5-HT1AR and 5-HT2AR signaling. The more pronounced effects of chronically used SSRIs on post-synaptic 5-HT1AR signaling is hypothesized to relate to their anti-stress, pro-coping properties but also their tendency to moderate or 'blunt' emotional responsiveness. The direct 5-HT2AR agonist properties of psychedelics are hypothesized to relate to their proclivity to enhance sensitivity to the environment as well as facilitate emotional release, which, when combined with psychological support, is hypothesized to be therapeutically potent.

depression and anxiety. Three DB-RC trials have assessed the impact of a single dose of psilocybin on depressive symptoms in patients with life-threatening cancer (Griffiths *et al*, 2016; Grob *et al*, 2011; Ross *et al*, 2016) and an open-label trial of psilocybin for treatment-resistant depression (TRD) has been completed (Carhart-Harris *et al*, 2016a,b). All four studies, and particularly the three most recent, found rapid, marked, and enduring anti-anxiety and depression effects post psilocybin. Significant improvements in obsessive compulsive disorder symptoms (Moreno *et al*, 2006) and alcohol dependence with psilocybin (Bogenschutz *et al*, 2015), anxiety with LSD (Gasser *et al*, 2014), and depression with ayahuasca (Osorio Fde *et al*, 2015; Sanches *et al*, 2016) help supplement the case for psilocybin and inspire questions regarding the potential generalized therapeutic action of psychedelics.

Focusing on antidepressant action, psilocybin, and psychedelics more generally, share some similarities with conventional antidepressants (ie, serotonergic modulation); however, they also possess some important differences. Regarding similarities, an altered relationship with the environment may be critical to recovery with selective serotonin reuptake inhibitors (Belsky, 2016; Harmer and Cowen, 2013) and heightened sensitivity to the environment is a cardinal feature of the psychedelic state (Carhart-Harris *et al*, 2015; Hartogsohn, 2016; Kaelen *et al*, 2015), perhaps due to psychedelics' direct agonist action at the 5-HT2AR (Dressler *et al*, 2016; Fiocco *et al*, 2007; Jokela *et al*, 2007). Regarding differences, the chronic antidepressant action of SSRIs includes reduced limbic responsiveness and emotional moderation or blunting, likely via post-synaptic 5-HT1A receptor signaling (Cowen and Browning, 2015; Deakin and Graeff, 1991; McCabe *et al*, 2010); this contrasts with the greater role for 5-HT2AR signaling with psychedelics, and emphasis on emotional release (Carhart-Harris *et al*, 2012b; Roseman *et al*, 2016; Watts *et al*, 2017). Contrasting approaches to emotion may be a fundamental difference between the SSRI and psychedelic treatment models (Figure 1).

In my opinion, if the science is allowed to progress without the kind of political interference that has hindered it in the past, psilocybin with psychological support (PwPS) will become an early option in the treatment of depression. I predict that PwPS will be found to have important areas of superiority over current early interventions such as SSRIs and CBT. Specifically, PwPS's rapid and enduring action with minimal exposure, positive side-effect profile, and specific therapeutic action—working to address rather than suppress or side-step aversive memories and emotions, may set it apart from the alternative, largely 'palliative' treatment options for major depression.

> *"That is the essence of science: ask an impertinent question, and you are on the way to a pertinent answer."* (Jacob Bronowski, 1908–1974)

Another consideration is that chronic antidepressant medication strategies appear to have a muting effect on psilocybin's acute and putative antidepressant effects (Bonson *et al*, 1996; Bonson and Murphy, 1996), implying that treating medication-heavy, treatment-resistant depressed patients with psilocybin will be especially challenging (Carhart-Harris *et al*, 2016a,b). Medication discontinuation would likely be required prior to receipt of the psychedelic and this often requires careful management (Baldwin *et al*, 2007).

THE THERAPEUTIC POTENTIAL OF PSYCHEDELIC DRUGS: UPBEAT PESSIMISM (GMG)

> *"What Leary took down with him was the central illusion of a whole life-style that he helped to create... a generation of permanent cripples, failed seekers, who never understood the essential old mystic fallacy of the Acid Culture: the desperate assumption that somebody, or at least some force, is tending the Light at the end of the tunnel."* (Hunter S Thompson. *Fear and Loathing in Las Vegas*, 1971)

Table 2 Clinical Trials Involving Psychedelics Published During the Present 'Second Wave' of Psychedelic Research

Study	Population/indication and sample size	Drug and design	Main efficacy outcome
Moreno *et al* (2006)	Obsessive compulsive disorder, $n=9$	Psilocybin: single-arm, within subjects, variable doses. Up to four doses of psilocybin	All patients showed improvements within 24 h of a treatment but no effect of dose
Grob *et al* (2011)	Anxiety and depression in end-stage cancer, $n=12$	Psilocybin: DB-RCT, crossover, inert placebo. Single dose of psilocybin	Significant reductions in trait anxiety at 3 months and depression at 6 months
Johnson *et al* (2014)	Long-term chronic tobacco smoking, $n=15$	Psilocybin: open-label. Up to three doses of psilocybin after four CBT sessions	80% of sample abstinent at 6 month follow-up
Gasser *et al* (2014)	Anxiety related to life-threatening disease, $n=12$	LSD: DB-RCT, crossover, very low dose (VLD) LSD = control. Single dose of LSD	Significant decreases in state and trait anxiety *vs* VLD at 2 months and sustained for 12 months
Bogenschutz *et al* (2015)	Alcohol dependence, $n=10$	Psilocybin: open-label. Up to two doses after seven motivational therapy sessions	Significant decrease in drinking behaviors for up to 9 months
Osorio Fde *et al* (2015) and Sanches *et al* (2016)	Major depressive disorder (MDD), $n=6$+study extension to $n=17$	Ayahuasca: open-label. Single dose of ayahuasca	Significant decreases in depressive symptoms for up to 21 days
Carhart-Harris *et al* (2016a,b)	Treatment-resistant MDD, $n=12$ +study extension to $n=20$	Psilocybin: open-label. Two doses of psilocybin	Significant decreases in depressive symptoms for up to 6 months
Ross *et al* (2016)	Anxiety and depression related to life-threatening cancer, $n=29$	Psilocybin: DB-RCT, crossover, niacin = active placebo. Single dose of psilocybin	Significant decreases in anxiety and depression *vs* niacin at 7 weeks (pre crossover) and sustained for 6.5 months
Griffiths *et al* (2016)	Anxiety and depression related to life-threatening cancer, $n=51$	Psilocybin: DB-RCT, crossover, VLD psilocybin = control. Single dose of psilocybin	Significant decreases in anxiety and depression *vs* VLD at 5 weeks (pre crossover). Effects sustained for 6 months

Abbreviations: DB-RCT, double-blind randomised controlled trial; VLD, very low dose; MDD, major depressive disorder; TRD, treatment-resistant depression.

FINDING SIGNAL AMIDST THE PSYCHEDELIC NOISE

As a clinician long committed to the view that neuroscience should inform psychiatry, psychedelics have always looked like a serious opportunity. Their structure and pharmacology inspired a generation of neurochemists to understand neurotransmitters and their receptors. And, the very idea that drugs could usefully change the experience of distressed patients with psychiatric disorders underpinned the revolution in psychopharmacology in the three decades from 1950. However, the 'illegal' status of psychedelics stopped serious research in humans until quite recently, as RLC-H has explained.

So, can psychedelics take us back to the future? I understand the appeal that RLC-H feels for their potential. However, the difficulty in finding a medical role for psilocybin must not be underestimated. It is worth reflecting on what we have learned from the very recently published clinical trials. Their strengths and their weaknesses define the challenge. As for the strengths, when two very similarly designed but independent studies of the effects of any pharmacological agent give the same result, it is encouraging. Accordingly, the two studies in patients with cancer experiencing enduring psychiatric symptoms and given psilocybin or a comparator (Griffiths *et al*, 2016; Ross *et al*, 2016) deserve to be taken seriously. However, there have to be caveats. Are we confident that we understand the patient population? Did the trial design allow a clear question to be asked and were the outcomes meaningful?

THE PATIENT POPULATION

In the choice of patient group, why cancer patients? Ross *et al* (2016) suggested that a domain of distress they call existential/spiritual well being is particularly relevant to depression in cancer while Griffith *et al* (2016) emphasize that evidence for efficacy of conventional medication or psychotherapy is poor or even negative.

Symptoms of both depression and anxiety are relatively common in cancer patients. But, they are often not very severe and in fact patients may choose not to seek help in their treatment (Baker-Glenn *et al*, 2011). In a case series of 128 patients attending for their first session of chemotherapy for cancer, only about 20% indicated they would appreciate psychological help for distress, depression, or anxiety. Of these, most indicated they would appreciate the opportunity to speak to someone—but only one suggested a psychiatrist.

Significant depressive symptoms can occur in cancer patients of course and active screening of a large consecutive cohort suggested about 8% met criteria for a major depressive episode (Sharpe *et al*, 2004) and many are not offered treatment. A subsequent trial in 200 such patients was conducted to compare a nurse intervention (which included antidepressant medication as an option and problem solving) with treatment as usual (Strong *et al*, 2008). There was a clinically significant and sustained impact of intervention on depressive symptoms (and on anxiety and fatigue): 68% of the treated group achieved remission compared with 45% of the comparator group (odds ratio 3 (confidence interval: 1.6–5.5).

Thus, the case for a particular unmet need in cancer patients is actually quite difficult to sustain. The idea that cancer diagnosis poses a particular threat to existential/spiritual well-being in some patients may be correct but there is a risk that one recruits into trials people with a particular interest in psychedelic experience, who are hence predisposed to endorse its benefits. They may not be representative of cancer patients in general. In the published study where it

is reported, the rate of previous use of hallucinogens was indeed high (55% in the Ross *et al*, 2016).

THE TRIAL DESIGN

In each of the two cancer studies, the design was a crossover, which compared, respectively, low-dose/high-dose psilocybin and niacin (placebo)/high-dose psilocybin. The subjective effects of the high dose consisted in heightened states of consciousness with marked emotional accompaniments (anxiety, tearfulness, and in a few cases, paranoid ideation). These effects were as expected, given the previous literature. It is difficult to see how blinding can be maintained because the subjective effects of drug were so florid. There was some uncertainty in the ratings by support staff, who supervised the sessions blind to dosing. However, overall one must assume the patients were usually unblinded by their experience on active drug. If so, it provided the kind of cue called a demand characteristic. That is anything that makes participants in an experimental study aware of what the experimenter expects to find or how participants are expected to behave. Such issues would also be difficult to avoid in judging outcomes, without great care in preserving raters to be blind.

THE OUTCOME MEASURES

The outcome measures of both trials are self, community, and clinician reports. Thus, they are entirely subjective, as most studies of antidepressants and anxiolytics have been. The demand problem has been noted already for patients, but it will also be problematic for third-party reports if patients communicate their own unblinding at interview. But, just as for other studies, symptoms alone are a problematic way of assessing outcome. In other words, they are not highly proximal to the disease process as for example research domain criteria dimensions have been suggested to be. But, they are also not distal enough for assessing the functional value of treatment either. More objective measures are possible. One could objectively measure simple motor activity or geolocation. Geolocation is particularly simple to obtain entirely passively from mobile phones. The resulting measure of time at home for example correlates well with depression severity in depressed bipolar patients (Palmius *et al*, 2016). In cancer patients, there is the further domain of medical care, which is known to be complicated by co-morbid depression. An increase in adherence to treatment or even efficacy could result from really effective treatment. Greater objectivity should contribute more to the picture in future research of psilocybin's potential role. Nevertheless, for the moment, subjective response remains the regulatory standard against which psychotropic drugs will be measured.

DOES THE PSILOCYBIN EXPERIENCE REALLY BELONG IN MEDICINE?

The unspoken assumption, which I think we both share, is that the use of psilocybin at this stage requires a medical justification. Certainly, it started in western society as a putative aid to psychotherapy, but of course, it has an older cultural history as a constituent of magic mushrooms. Many believed and believe that the justification for the use of such drugs lies in their capacity to open the doors of perception, as Aldous Huxley put it. On this view, access to such drugs should be a recreational right, like access to alcohol, cigarettes, and increasingly cannabis. As with cannabis, medical use may be expected to promote wider discretionary use for any reason. Some may still regard this as a red light for the development of medical indications.

However, there is an important corollary to the continuing illegal status of psychedelics. It seems to me paradoxical, even incredible, that such drugs should not be available for medical use in conditions for which euthanasia is already available. In Belgium, neuropsychiatric disorders were first reported under euthanasia legislation in 2004/5. Of the first such 100 patients considered for euthanasia between 2007 and 2011, 58 had depression. Forty-eight of the total were accepted for euthanasia (35 completed) and six others had died by suicide within 12 months from the end of the study. Most patients were female, aged 40–60 years. Euthanasia for psychological suffering is similarly available in the Netherlands and Luxemburg (Thienpont *et al*, 2015).

So, I think we need psilocybin in medicine but we should not forget the failures of human logic, which mean we need high-quality clinical trials:

> *"All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases."* (Galen in 180 AD)

HOW TO MOVE THE FIELD FORWARD (GMG AND RLC-H)

Our shared interest in the development of psychedelics, and particularly psilocybin, for medical use is a major point of convergence. There may be a subtle difference in our views of the so-called 'mystical' elements of the psychedelic experience, ie, both of us see the term 'mystical' as problematic—but whereas GMG views the acute 'psychedelic experience' as irrelevant to the clinical development of psychedelics, RLC-H sees it as a potentially exploitable component—especially as it has been shown to be predictive of long-term clinical outcomes (eg, in Johnson *et al*, 2014; Bogenschutz *et al*, 2015; Griffiths *et al*, 2016; Ross *et al*, 2016; Carhart-Harris *et al*, 2016a,b). Perhaps the most notable point of divergence, however, relates to the choice of patient population for the clinical development of psilocybin for depression. For GMG, the most obvious and relevant unmet need is treatment-resistant depression (see below), and while RLC-H accepts that treatment resistance is often the first port-of-call for the development of a novel intervention, he feels that unipolar depression more generally, will prove a better indication for this treatment. In his view, psilocybin will be safest, most effective, and easiest to implement, prior to the treatment-resistant stage of illness.

Focusing on treatment-resistant depression for the moment, however, we both recognize that a significant number of patients treated first line with either a SSRI or CBT fail to respond adequately (Gaynes, 2009). Persisting symptoms lead to enduring chronicity of depression, and there is no consensus in existing guidelines on what to do

next. Moreover, the efficacy of secondary intervention is often modest and new medications can introduce new side effects. The duration of distress with TRD and its economic impact are considerable. We agree that TRD represents a valid point in the treatment pathway, where a single psychedelic intervention might find a place; however, RLC-H questions whether patients must wait until their depression is significantly stamped-in before psilocybin can be considered, and based on the speed and duration of treatment responses seen in the trials listed above, it seems reasonable to ask whether early intervention with psilocybin could be prophylactic—and there is also the issue of SSRIs obstructing the potential therapeutic action of psilocybin.

If it is to be TRD, however, then patient recruitment can be based on pre-existing criteria (Sackeim, 2001) and patients meeting them will not be rare and should not be excessively treatment resistant. As noted earlier, there is a significant challenge to the issue of continuing medication, most commonly with SSRIs. There is anecdotal evidence that psychedelic effects are largely attenuated by ongoing treatment with SSRIs (Bonson *et al*, 1996) and perhaps with other antidepressants (Bonson and Murphy, 1996). Down-regulation of 5-HT2A receptors is a feature of many different first-line antidepressant drugs (Muguruza *et al*, 2014), as well as second-line antidepressant medications (eg, atypical antipsychotics) with significant 5-HT2AR antagonist properties (Gray and Roth, 2001). Any trial would ideally be conducted in patients withdrawn from such drugs for at least 2 weeks or so, but we accept that this is not always straightforward (Baldwin *et al*, 2007).

Moving on from questions of the optimal patient population, both of us can see merit in a multiple dose trial comparing, for example, 1, 10 and 25 mg of psilocybin. Such a design seems to overcome some of the problems any trial of a psychedelic will face. The ethical problem of equipoise seems satisfactory because we really do not know which dose, if any, will be effective, and patients can enter the study knowing that whatever group they are allocated to, they will receive active drug. The omission of a strict placebo control would be pragmatic in this sense, as expectation and preparation would be standardized. We know the highest dose of psilocybin will likely unblind participants and the expectation of a possible placebo would complicate recruitment. An approximation to an inert placebo condition may be met with the 1 mg psilocybin arm, as such a dose is likely too low to produce appreciable subjective or physiological effects (Griffiths *et al*, 2016). The differences between a dose mainly producing perceptual distortion (10 mg) and one more capable of producing the more profound, putatively 'transformative' aspects of the psychedelic experience (25 mg) is also of scientific and clinical interest.

Comparing mechanisms and/or efficacy with an established treatment would be a next step to advance the evidence base for psilocybin for TRD. For example, psilocybin could be compared with ketamine since it has some similarities: rapid, single-dose efficacy, and obvious subjective effects during its infusion. Psilocybin's distinctive subjective effects and the implications of this for blinding would still remain a major challenge; moreover, as with ketamine, there will also remain the question of how much an acute response is sustained and whether a maintenance dose may be required.

The traditional view of the mechanism, whereby psilocybin works, emphasizes the importance of accompanying psychotherapy (Johnson *et al*, 2008; Richards, 2015). Accordingly, psychedelics administered without psychological support and/or a supportive environment may have limited antidepressant efficacy, and in very rare cases, could even worsen a patient's condition (Oram, 2014). We share the view that the presence of psychological support is an essential component of the psychedelic treatment model (Johnson *et al*, 2008) but we also recognize that the magnitude and nature of its contribution needs to be better defined and tested.

Pragmatically, we accept that minimizing the active psychological work of the therapy would be desirable (eg, therapy time is expensive) and scientifically, doing so would allow drug effects and dose to be better identified. Critically however, any such therapy minimization should not be allowed to jeopardize patient safety (Johnson *et al*, 2008). A future challenge will be to learn how psychological interventions can maximize the advantages of the psychedelic state. For example, we can imagine how cognitive therapy, attentional-bias training and/or de-sensitization could be investigated with or without psilocybin assistance.

In other respects, a psilocybin trial is easier to conduct than studies requiring continuing adherence to a daily oral dose of an antidepressant. Exposure to the treatment can be completely controlled and follow-up can be relatively pragmatic. It seems logical to determine an early proximal end point to prove initial impact of treatment and then to follow subsequent illness course as comprehensively as possible. In this way, we will be able to determine time to supplementary treatment, document recovery of symptoms and function, and perhaps objectify improvement using a simple frictionless measure of activity-like geolocation (Palmius *et al*, 2016).

In the short term, there will also be a need to demonstrate cost effectiveness. The requirement for psychological support and/or a supportive environment could be a major limitation of the psychedelic treatment model. However, direct medical costs need to be netted off against the social and economic costs of illness.

In summary, a door has been opened for the medical repurposing of psychedelics. The possibility exists that drugs like psilocybin can meet a major unmet need in the treatment of psychiatric disorders. For GMG, treatment-resistant depression is the most logical place to start because of the uncertainty around the choice of next-step treatment after an SSRI fails, and while RLC-H accepts this (Carhart-Harris *et al*, 2016a,b), he looks forward to a time when an individual may receive psilocybin before the ruts of depression are allowed to deepen (Holtzheimer and Mayberg, 2011). Regardless of who the 'right' patient population might be eventually, a key challenge now is to design the optimal trial to demonstrate efficacy, agree its validity with regulatory authorities and fund it.

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