Circumspective

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Title: The therapeutic potential of psychedelic drugs: past, present and future

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Abstract

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 aides 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 programmes. 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 3 separate clinical trials of psilocybin for depressive symptoms. In this Circumspective piece, Robin Carhart-Harris and Guy Goodwin 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.

The therapeutic potential of psychedelic drugs: tempered optimism (Robin Carhart-Harris)

> *"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

Psychedelics* drugs awakened a significant cultural zeitgeist in mid-20th century (Stevens, 1987, see table 1). Catalysed 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 & 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 & Bakalar, 1979; Lee & Shlain, 1992; Stevens, 1987).

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 & Johnson, 1950
c. 1953	ACNP Founding president Joel Elkes (1961) publishes on LSD after openly self-experimenting with it	Bradley, Elkes & Elkes, 1953; Roberts, 2008
1954	Aldous Huxley's 'The Doors of	Huxley, 1954

	Perception' published: documents mescaline self-experiment	
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
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 centre stage at 1964 APA meeting - opinions polarised	Mangini, 1998; Cole & Katz, 1964
1965	Sandoz stop manufacture of LSD and psilocybin	Stevens, 1987
1966	Prohibition on psychedelics and curtailment of research begins in US; Senator Robert Kennedy questions its logic	Stevens, 1987; Lee & Shlain, 1992

Table 1. Notable landmarks of mid 20th Century psychedelic research

The present revival

Human psychedelic research fell into a 25 year hiatus before scientists in Germany (Hermle et al., 1992), the US (Strassman & Qualls, 1994) and Switzerland (Vollenweider, Leenders, Scharfetter, Maguire, Stadelmann & Angst, 1997) began its revival. There now exists a foundation of human neuroimaging (Carhart-Harris et al., 2012a; Carhart-Harris et al., 2016d; Daumann, Wagner, Heekeren, Neukirch, Thiel & Gouzoulis-Mayfrank, 2010; Muthukumaraswamy et al., 2013; Palhano-Fontes et al., 2015; Preller et al., 2017; Riba, Anderer, Jane, Saletu & Barbanoj, 2004; Riba, Romero, Grasa, Mena, Carrio & Barbanoj, 2006; Vollenweider, Leenders, Scharfetter, Maguire, Stadelmann & Angst, 1997), psychology (Carhart-Harris et al., 2016c; Carhart-Harris, Kaelen, Whalley, Bolstridge, Feilding & Nutt, 2015; Carter, Hasler, Pettigrew, Wallis, Liu & Vollenweider, 2007; Gouzoulis-Mayfrank et al., 2005; Griffiths, Richards, McCann & Jesse, 2006; MacLean, Johnson & Griffiths, 2011; Schmid et al., 2015) and psychopharmacology studies with

psychedelics (Kometer, Schmidt, Bachmann, Studerus, Seifritz & Vollenweider, 2012; Preller et al., 2017; Valle et al., 2016; Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel & Hell, 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 (OCD) (Moreno, Wiegand, Taitano & Delgado, 2006), psilocybin and LSD for end-of-life psychological distress (Gasser et al., 2014b; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), psilocybin for alcohol (Bogenschutz, Forcehimes, Pommy, Wilcox, Barbosa & Strassman, 2015b) and tobacco addiction (Johnson, Garcia-Romeu, Cosimano & Griffiths, 2014) and ayahuasca (Osorio Fde et al., 2015) and psilocybin for major depressive disorder (Carhart-Harris et al., 2016). 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. Guy Goodwin critically discusses two of the largest and better designed trials in the next section (Griffiths et al., 2016; Ross et al., 2016).

Study	**Population/indication and sample size**	**Drug & design**	**Main efficacy outcome**
Moreno et al. (2006)	Obsessive compulsive disorder, n = 9	Psilocybin: single-arm, within subjects, variable doses. Up to 4 doses of psilocybin	All patients showed improvements within 24 hours of a treatment session but no effect of dose
Grob et al. (2011)	Anxiety and depression in end-stage cancer, n = 12	Psilocybin: DB-RCT, cross-over, 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 3 doses of psilocybin after 4 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, cross-over, very low dose (VLD) LSD = control. Single dose of LSD	Significant decreases in state and trait anxiety at 2 months after full LSD dose versus VLD and sustained for 12 months
Bogenschutz et al. (2015)	Alcohol dependence, n = 10	Psilocybin: open-label. Up to 2 doses after 7 motivational therapy sessions	Significant decrease in drinking behaviours for up to 9 months post-treatment
Osorio Fde et al. (2015) & 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 post-

			treatment
Carhart-Harris et al. (2016a & 2016e)	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 post-treatment
Ross et al. (2016)	Anxiety and depression related to life-threatening cancer, n = 29	Psilocybin: DB-RCT, cross-over, niacin = active placebo. Single dose of psilocybin	Significant decreases in anxiety and depression vs niacin at 7 weeks (pre crossover). Effects sustained at 6-7 months follow-up
Griffiths et al. (2016)	Anxiety and depression related to life-threatening cancer, n =	Psilocybin: DB-RCT, cross-over, VLD psilocybin = control. Single dose of psilocybin	Significant decreases in anxiety and depression after full-dose vs VLD at 5 weeks (pre crossover). Effects sustained at 6 month follow-up

Table 2. Modern clinical trials involving psychedelics. DB-RCT = double-blind randomised controlled trial. VLD = very low dose. MDD = major depressive disorder. TRD = treatment-resistant depression.

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 & Nutt, 2010; Waldman, 2017). Contrary to the alarmist campaigning that so negatively affected perceptions of psychedelics after the 1960s, subjective (Carhart-Harris & Nutt, 2010; Carhart-Harris & Nutt, 2013; van Amsterdam, Nutt, Phillips & van den Brink, 2015), naturalistic/observational (Bouso et al., 2012) and population-based data (Hendricks, Thorne, Clark, Coombs & Johnson, 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 & 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, Jelen, Flynn, Frowde & Young, 2016). Moreover, a meta-analysis of studies of LSD for alcoholism performed in the 50s-60s was similarly supportive of its potential (Krebs & Johansen, 2012). The absence of standardised diagnostic techniques, measures of symptom severity and lack of

randomisation 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 randomised controlled (DB-RC) study compared the acute and longer-term psychological effects of single high doses of psilocybin (30mg) and methylphenidate (40mg) 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, Richards, McCann & Jesse, 2006). Since then, the focus has shifted to include patients with symptoms of 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; 2016e). All four studies, and particularly the three most recent, found rapid, marked, and enduring anti-anxiety and depression effects post-psilocybin. Significant improvements in OCD symptoms (Moreno, Wiegand, Taitano & Delgado, 2006) and alcohol-dependence with psilocybin (Bogenschutz, Forcehimes, Pommy, Wilcox, Barbosa & Strassman, 2015a), anxiety with LSD (Gasser et al., 2014a), 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 (i.e. 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 & Cowen, 2013) and enhanced sensitivity to the environment is a cardinal effect of psychedelics (Carhart-Harris, Kaelen, Whalley, Bolstridge, Feilding & Nutt, 2015; Hartogsohn, 2016; Kaelen et al., 2015), perhaps due to their direct action at the 5-HT2AR (Dressler, Balieiro, Ferreira de Araujo, Silva & Ernesto Dos Santos, 2016; Fiocco, Joober, Poirier & Lupien, 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 signalling (Cowen & Browning, 2015; Deakin & Graeff, 1991; McCabe, Mishor, Cowen & Harmer, 2010); this contrasts with the greater role for 5-HT2AR signalling with psychedelics, and emphasis on emotional *release* (Carhart-Harris et al., 2012b; Roseman et al., 2017; Watts et al., 2017). Contrasting approaches to emotion may be a fundamental difference between the SSRI and psychedelic treatment models (fig. 1).

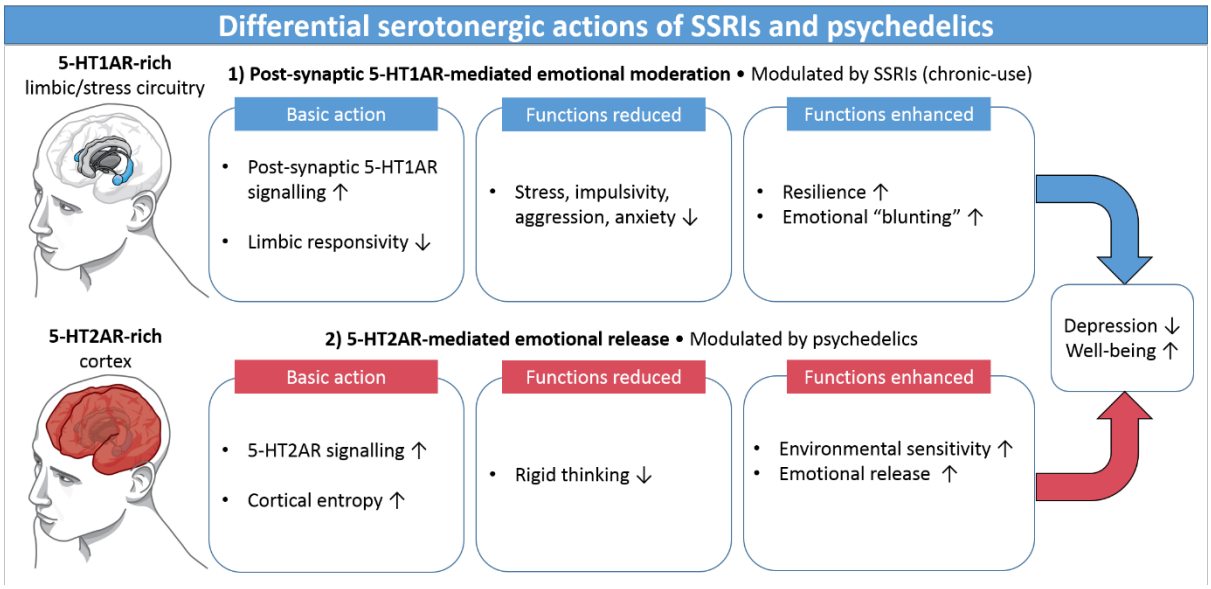

Figure 1. A bipartite model of serotonergic functioning focused on the effects of post-synaptic 5-HT1AR and 5-HT2AR signalling. The more pronounced effects of chronically-used SSRIs on post-synaptic 5-HT1AR signalling is hypothesised to relate to their anti-stress, pro-coping properties but also their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

In my opinion, if the science is allowed to progress without the political interference that has dogged 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, Buckholtz & Murphy, 1996; Bonson & Murphy, 1996), implying that treating medication-heavy, treatment-resistant depressed patients with psilocybin may be especially challenging (Carhart-Harris et al. 2016a; 2016e). Medication discontinuation would likely be required prior to receipt of the psychedelic and this often requires careful management (Baldwin, Montgomery, Nil & Lader, 2007).

*__Footnote__: *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.

The therapeutic potential of psychedelic drugs: upbeat pessimism (Guy Goodwin)

> *"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)

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 Robin has explained.

So, can psychedelics take us back to the future? I understand the appeal that Robin 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. suggested that a domain of distress they call existential/spiritual well-being is particularly relevant to depression in cancer while Griffith et al. 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, Park, Granger, Symonds & Mitchell, 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.).

The trial design

In each of the two cancer studies, the design was a cross-over 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 (RDoC) 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 aide 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 6 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, Verhofstadt, Van Loon, Distelmans, Audenaert & De Deyn, 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 (Guy Goodwin and Robin Carhart-Harris)

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 divergence between us regarding the so-called 'mystical' elements of the psychedelic experience, i.e. both of us see the term 'mystical' as problematic - but whereas Guy views the acute 'psychedelic experience' as irrelevant to the clinical development of psychedelics, Robin sees it as a potentially important and 'exploitable' component – especially as it has been shown to be predictive of long-term clinical outcomes (e.g. in Johnson et al., 2014; Bogenschutz et al., 2015; Griffiths et al., 2016 & Ross et al., 2016; Carhart-Harris et al., 2016e). Perhaps the most notable point of divergence however, relates to the choice of patient population for the clinical development of psilocybin for depression. For Guy, the most obvious and relevant unmet need is treatment resistant depression (see below), and while Robin 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 recognise 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, Robin 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, he wonders 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, Buckholtz & Murphy, 1996) and perhaps with other antidepressants (Bonson & 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 (e.g. atypical antipsychotics) with significant 5-HT2AR antagonist properties (Gray & Roth, 2001). Any trial would ideally be conducted in patients withdrawn from such drugs for at least two weeks or so, but we accept that this is not always straightforward (Baldwin, Montgomery, Nil & Lader, 2007).

Moving on from questions of the optimal patient population, both of us can see merit in a multiple dose trial comparing e.g. 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 standardised. 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 1mg psilocybin arm, as such a dose is likely too low to produce appreciable subjective effects (Griffiths et al., 2016). The differences between a dose mainly producing perceptual distortion (10mg) 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 potent and idiosyncratic subjective effects and the implications of this for blinding would still remain a major challenge. As with ketamine, there will also remain the question of how much an acute response is sustained, whether a maintenance medication may be required and, if so, which one.

The traditional view of the mechanism whereby psilocybin works, emphasizes the importance of accompanying psychotherapy (Johnson, Richards & Griffiths, 2008; Richards, 2015). Accordingly, psychedelics administered without psychological support and/or a supportive environment may have limited antidepressant efficacy, and in 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, Richards & Griffiths, 2008) but we also recognise 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 (e.g. therapy time is expensive) and scientifically, doing so would allow drug-effects and dose to be better identified. Critically however, any such therapy-minimisation should not be allowed to jeopardise patient safety (Johnson, Richards & Griffiths, 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 endpoint 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 re-purposing of psychedelics. The possibility exists that drugs like psilocybin can meet a major unmet need in the treatment of psychiatric disorders. For Guy, 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 Robin accepts this (Carhart-Harris et al., 2016a; 2016e), he looks forward to a time when an individual may receive psilocybin before the ruts of depression are allowed to deepen (Holtzheimer & 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.

Declaration of conflicting interests

GMG is a NIHR senior investigator; the views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

GMG holds a grant from Wellcome Trust, holds shares in P1vital and has in the past 3 years

served as consultant, advisor or CME speaker for Angelini, MSD, Lundbeck (/Otsuka or /Takeda), Medscape, P1Vital, Pfizer, Servier and Shire.

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RLC-H and GMG are currently advising Compass Pathways, a commercial initiative to develop psilocybin as a medicine.

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