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Review

Psychedelics in the treatment of unipolar mood disorders: a systematic review

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James JH Rucker[1,2*], Luke A Jelen[1,3*], Sarah Flynn[4], Kyle D Frowde[4] and Allan H Young[1,3]

Abstract

Unipolar mood disorders, including major depressive disorder and persistent depressive disorder (dysthymia), confer high rates of disability and mortality and a very high socioeconomic burden. Current treatment is suboptimal in most cases and there is little of note in the pharmaceutical development pipeline. The psychedelic drugs, including lysergic acid diethylamide and psilocybin, were used extensively in the treatment of mood disorders, and other psychiatric conditions, before their prohibition in the late 1960s. They are relatively safe when used in medically controlled environments, with no reported risk of dependence. Here, we present a systematic review of published clinical treatment studies using psychedelics in patients with broadly defined UMD, and consider their place in psychiatry. Whilst all of the included studies have methodological shortcomings, of 423 individuals in 19 studies, 335 (79.2%) showed clinician-judged improvement after treatment with psychedelics. A recently completed pilot study in the UK favours the use of psilocybin with psychological support in treatment resistant depressive disorder. The evidence overall strongly suggests that psychedelics should be re-examined in modern clinical trials for their use in unipolar mood disorders and other non-psychotic mental health conditions.

Keywords

Depression, dysthymia, psychedelics, psilocybin, LSD

Introduction

Unipolar mood disorders (UMD), including major depressive disorder (MDD) and persistent depressive disorder (PDD; previously known as dysthymia), are common psychiatric disorders associated with high morbidity, high socio-economic burden and high rates of completed suicide (Greenberg et al., 1993; Harris and Barraclough, 1998; Kessler et al., 2003). The lifetime prevalence of MDD and PDD are conservatively estimated to be 6.7% and 3.6%, respectively (Waraich et al., 2004) and UMD is estimated to become the second leading cause of disability worldwide by 2020, second only to heart disease (Murray and Lopez, 1997). UMDs are frequently recurrent. PDD, by definition, lasts over 2 years and is often unremitting. Of those who have had an episode of MDD requiring psychiatric input, 80% will have another (Kessler et al., 2003) and the more episodes suffered the higher the likelihood of a further episode (Keller et al., 1982; Zis and Goodwin, 1979). In a large study using four successive medical treatment steps, 67% of patients eventually achieved remission (Rush and Trivedi, 2006), although the remainder, 33%, did not. Those who do not respond to multiple treatments have a poor prognosis that contributes to a disproportionate amount of socioeconomic burden, justifying calls for a research focus on novel therapeutic interventions (Cleare et al., 2015). Established but controversial therapies for resistant cases, such as electroconvulsive therapy and psychosurgery, are not effective in all cases, carry substantial stigma and the risk of significant side effects leads many patients to discount them as potential treatment options. Many pharmaceutical companies have ended research efforts into psychiatric disorders, and there are few novel agents in development (Hyman, 2013; Miller, 2010), leading some to look to history for inspiration. The dissociative drug ketamine has recently been investigated in this regard, however whilst there is some evidence for its use as a rapidly acting antidepressant, the effects appear to be transient, chronic usage has been associated with urinary tract problems and the drug has an established and concerning potential for abuse (Naughton et al., 2014).

Psychedelic compounds, particularly lysergic acid diethylamide (LSD) and psilocybin, were used and researched extensively in psychiatry before legal prohibition in 1967 (Grof, 2008). The drugs were initially noted to induce a temporary state of mind that was not dissimilar to psychosis. Whilst this suggested (and more formal research confirmed) that they were probably not useful for those with established psychotic disorders, or for those at high risk of developing them, patients suffering from so-called 'neurotic' disorders, characterized by constrained, entrenched and often negative patterns of thought, feeling and behaviour, often reported new insights under the influence of

[1]The Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[2]South West London and St George's Mental Health NHS Trust, London, UK
[3]South London and Maudsley NHS Foundation Trust, London, UK
[4]King's College London School of Medicine, London, UK

*These authors contributed equally to this manuscript

Corresponding author:
James JH Rucker, The Institute of Psychiatry, Psychology and Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF, UK.
Email: james.rucker@kcl.ac.uk

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psychedelics when taken in therapeutically supportive settings. Patients sometimes also described transformative states of mind that allegedly conferred long-lasting beneficial change (Grof, 2008), and which appeared to share some similarities with the states sought within the spiritual, religious and ceremonial uses of psychedelics, for which evidence stretches back to the dawn of recorded human history (Bruhn et al., 2002; Ott and Bigwood, 1978). As well as research in neuroses, covered in this review, an extensive research program on the use of LSD in the psychotherapeutic treatment of alcoholism was established, most notably in Canada (Dyck, 2006), and in the physical and existential pains experienced with terminal cancer at the Maryland Psychiatric Research Centre in North America (Grof and Halifax, 1977). The quality of many studies was suboptimal by modern standards, with the best quality research found in alcoholism. A recent meta-analysis of six good quality controlled trials of LSD treatment in alcoholism found that LSD treatment was favoured over placebo with an odds ratio of 1.96 (95% confidence interval (CI) 1.36–2.84, $p = 0.0003$) (Krebs and Johansen, 2012).

Politically motivated and media-driven demonization of psychedelics in the 1960s and 1970s, alongside medical concern for the occasionally harmful sequelae of recreational use in psychologically destabilizing environments, has led to them being amongst the most stigmatized and legally restricted of all psychoactive compounds. However, they do not induce dependence (Brunton et al., 2011), and are physiologically (Gable, 2004) and psychologically (Cohen, 1960; Strassman, 1984) safe when used in medically controlled settings. Indeed, two separate, modern population studies have associated their use with a *lower* incidence of mental health problems and no increased risk of psychosis (Hendricks et al., 2015; Johansen and Krebs, 2015). They remain classified under Schedule I of the UN classification of drugs, severely restricting their use in research and entirely preventing their use in medical practice, a classification that has been recently questioned (Nutt et al., 2013; Rucker, 2015).

Since the turn of the millennium, there has been an upsurge in interest in the mechanism of action of psychedelics and their therapeutic utility in a broad range of mental health problems, including UMDs. Investigations of their pharmacology (Passie et al., 2002; 2008), molecular neurobiology (Aghajanian and Marek, 1999; Halberstadt and Geyer, 2011; Moreno et al., 2011; Vollenweider and Kometer, 2010), neuroimaging correlates (Carhart-Harris et al., 2012; Carhart-Harris et al., 2016) and therapeutic mechanisms (Bogenschutz and Pommy, 2012; Loizaga-Velder and Verres, 2014; Maji et al., 2015; Tupper et al., 2015) have been published. The reviews of Nichols are particularly comprehensive (Nichols, 2004; 2016). Safety guidelines for the use of psychedelics in modern clinical research settings are also available (Johnson et al., 2008) and pilot clinical studies in anxiety associated with advanced cancer (Gasser et al., 2015; Grob et al., 2011), obsessive compulsive disorder (Moreno et al., 2006), tobacco (Johnson et al., 2014) and alcohol (Bogenschutz et al., 2015) addiction and cluster headaches (Sewell et al., 2006) have been completed over the last 10 years, with encouraging results. Some have also argued that psychedelics may confer new insights into the nature of psychotic disorders such as schizophrenia (González-Maeso and Sealfon, 2009) and wider theories of brain function (Carhart-Harris and Friston, 2010).

In this paper, we systematically collated the pre-prohibition literature on the therapeutic use of psychedelics on broadly defined unipolar mood disorder, within which we include contemporary depressive disorder with co-morbid anxiety, as well as disorders grouped under the old-fashioned terms 'neurotic' and 'psychoneurotic' disorders. This is with the aim of evidencing the debate on whether these substances should be reinvestigated with the benefit of modern, more systematic trial methodology. Pre-prohibition literature is described and synthesized and this is used to inform a discussion on the benefits and challenges of integrating contemporary psychedelic research into modern clinical trial designs.

Methods

The PsycINFO and MEDLINE databases (1940–2000) were searched using the following terms: *LSD, lysergic acid diethylamide, psychedelic* or *hallucinogen* and *therapy, psychotherapy* or *treatment.* The 'Multidisciplinary Association for Psychedelic Studies' (MAPS) Psychedelic Bibliography contains a comprehensive overview of psychedelic research, including a complete list of all studies on the therapeutic use of psychedelics from 1931–1995 (MAPS, 2016). This database was also manually searched to find titles or abstracts including the above search terms. A total of 2303 papers were identified through electronic records and other sources, representing 2010 papers after removal of duplicates. 1,901 of these were excluded after screening of the titles or abstracts, leaving 109 that were screened in more detail for eligibility. Of these, 88 were excluded to leave the 21 papers used in this systematic review.

Search results were screened by reading the titles and abstracts. More detailed review of each potentially relevant paper identified clinical studies referring to the use of LSD in the treatment of '*Depressive'*, '*Neurotic'* and '*Psychoneurotic'* patients. Subsequent examination of reference lists identified other potential eligible studies or review articles. Where studies referred to the treatment of multiple patient populations, results of treatment for these selected groups were extracted. The findings are summarized in Table 1.

Description of studies

In the first report on the therapeutic use of LSD in 1949, Condrau proposed its use as an antidepressant based on the euphoric properties of the drug (Condrau, 1949). Through the administration of small and progressively increasing daily doses he explains that although some depressed patients showed some improvement in mood following LSD treatment, the results were not convincing and he felt the observed changes did not exceed the limits of spontaneous variation. A similar study by Savage, using daily doses of 20–100 μg of LSD in 15 patients with depressive reactions, reported that 3 recovered fully and 4 others improved after 1 month of treatment (Savage, 1952).

The first group to use LSD as an adjunct to traditional psychotherapy were Busch and Johnson (1950). During LSD therapy, five psychoneurotic patients all had experiences which the authors felt profoundly influenced the course of their illness, with two of the patients improving sufficiently to discontinue treatment. However, there is no indication in the paper as to the frequency and number of sessions or the specific techniques used.

The approach of periodic low dose use of LSD combined with psychotherapy later came to be known as the 'psycholytic' approach. This method was pursued by Sandison and colleagues who, in 1954, published the results of treatment in 36 patients

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Table 1. Summary of studies included in the systematic review.

Author	Year	Sample size (*n*)	Population	Dose range	Frequency of sessions	Number of sessions	Percentage improvement (*n*)
Condrau	1949	5	'Depressives'	'Daily increasing'	Daily	Several	40% (2)
Busch and Johnson	1950	5	'Psychoneuroses'	30–40 µg	*Unknown*	*Unknown*	40% (2)
Savage	1952	15	'Depressives'	20–100 µg	Daily	Up to 30	47% (7)
Sandisonet al.*	1954	30	'Neurotics' and 'Depressives'	25–400 µg	Weekly	2–40	90% (27)
Sloane and Lovett Doust	1954	12	'Depression'	40–120 µg	Once	1	*Unclear*
Langner and Kemp	1956	19	'Psychoneuroses'	*Unknown*	*Unknown*	*Unknown*	58% (11)
Martin	1957	22	'Psychoneuroses'	40–160 µg	Weekly	2–13	91% (20)
Sandison and Whitelaw*	1957	35	'Psychoneurotic depression' and 'Primary anxiety neurosis'	50–200 µg	Weekly	Up to 30	71% (25)
Lewis and Sloane	1958	11	'Psychoneuroses'	25–500 µg	Biweekly–weekly	1–25	64% (7)
Eisner and Cohen	1958	5	'Depressive reactions'	25–100 µg	Weekly	2–6	80% (4)
Chandler and Hartman	1960	44	'Psychoneuroses'	25–150 µg	1–6 weeks	1–26	*Unclear*
Maclean et al.	1961	25	'Anxiety' and 'Depressive reaction neuroses'	400–1500 µg	Once	1	92% (23)
Sherwood et al.	1962	7	'Neuroses'	100–200 µg LSD and 200–400 mg Mescaline	Once	1	57% (4)
Martin	1964	60	'Severe neurotics'	*Unknown*	Weekly	Mean = 20	95% (57)
Geert-Jörgensen et al.	1964	28	'Anxiety neuroses', 'Depressive neuroses' and 'Endogenous depression'	50–400 µg	*Unknown*	5–58	68% (19)
Whitaker	1964	21	'Depression'	100–250 µg	*Unknown*	Mean = 3.28	81% (17)
Savage	1966	77	'Neurotics' and 'Depressives'	200–300 µg LSD ± 200–300 mg Mescaline	Once	1	80% (62)
Savage et al.	1967	36	'Psychoneurotic depressive reaction'	200–300 µg LSD ± 200–400 mg Mescaline	Once	1	81% (29)
Baker	1967	11	'Depressives'	100–2000 µg	Weekly	1–10	91% (10)
Leuner	1967	11	'Depressive reactions'	30–200 µg	Biweekly–weekly	2–16	82% (9)
Savage et al.	1973	63	'Severe chronic neuroses'	50 µg or 350 µg	Once	1	*Unclear*

*There are overlapping populations in the studies of Sandison 1954 and 1957.

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with psychoneuroses in a hospital setting (Sandison et al., 1954). Treatments occurred at weekly intervals. For the scope of this review, six patients were excluded: four conversion hysteria, one homosexuality, one schizoid personality. Researchers started LSD treatment at 25 μg and gradually increased the dose in subsequent sessions until an 'adequate reaction' was obtained. Treatment was repeated once a week and after 2–4 weeks the team decided whether sessions continued in the outpatient setting or whether the patient remained in hospital. Out of the 30 patients included in this review the authors report that 12 recovered and 15 others showed some degree of improvement.

This team published a subsequent paper 3 years later with further results from a total of 100 patients that had been treated to date (Sandison and Whitelaw, 1957). Improvement in 25 out of 35 patients described as suffering from 'psychoneurotic depression' or 'primary anxiety neuroses' was seen. Unfortunately, it was impossible to differentiate the findings for patients in the first study from the cumulative total so there will be a degree of overlap in the reported data from these two papers in Table 1. The authors conclude that LSD appears to be of, 'utmost value in psychotherapy, both in cases otherwise resistant to treatment and as a method of avoiding the prolonged time necessary for a full psychological analysis'. (Sandison and Whitelaw, 1957).

In an attempt to obtain objective estimates of some of the physiological and psychological changes produced, Sloane and Lovett Doust administered LSD to 11 healthy controls, 12 patients with predominant depression and 7 patients with schizophrenia at doses between 40 μg-120 μg (Sloane and Lovett Doust, 1954). Although three of the depressive patients showed some lightening of their mood, the authors conclude, 'it proved difficult to obtain valid differentiating measures of clinically apparent changes'.

Langner and Kemp give a brief report on their results of over 500 LSD psychoanalytic treatment sessions in 40 patients (Langner and Kemp, 1956). Although no specific technique or dosing is described, they claim that in a group of 'psychoneurotics,' recovery or marked improvement was seen in 11 out of 19 patients.

Assessing the potential use and feasibility of LSD in the treatment of chronic psychoneurotic disorders under day-patient conditions, Martin describes further promising results (Martin, 1957). Patients arriving at the unit in the morning were given an initial dose of 25-50 μg that increased slightly with each treatment until an optimal reaction was obtained. The sessions were terminated by giving 50 mg chlorpromazine, 6 hours after the initial LSD dose and the patient was then permitted to travel home accompanied by a friend or relative by the end of the day. The authors note that some patients became more readily 'accessible' under LSD and suggest that its therapeutic effect is in part due to the reliving of early experiences and release of repressed feelings. Although the study describes the treatment of 50 patients with chronic psychoneurosis this review excluded 28 patients described as 'psychopaths', 'sexual neurotics' and 'obsessional'. Those remaining were described as suffering from 'chronic tension states' and, in this group of 22 patients, although only 1 had fully recovered, 19 others showed significant improvement.

Working with a group of 23 psychiatric inpatients, Lewis and Sloane report results no better than those obtained with other treatments (Lewis and Sloane, 1958). However, excluding those with schizophrenia and 'obsessional illness' gives more favourable results in the remaining 11 patients with 'psychoneuroses', in which a total of 7 showed improvement. Again the authors concluded that, 'the drug provided a useful aid to the psychotherapeutic technique' (Lewis and Sloane, 1958). In another study from the same year, Eisner and Cohen administered LSD to 22 patients weekly for an average of 5–6 weeks (Eisner and Cohen, 1958). The authors suggest that those with depressive states appear to be very suitable for treatment, with improvement seen in 80% of patients (four out of five) suffering from 'depressive reactions' after a follow up period of 6–18 months.

Further investigating the use of LSD as a facilitating agent in psychotherapy, Chandler and Hartman report on their work in 110 patients in whom LSD was utilized as part of their treatment (Chandler and Hartman, 1960). The patient population included 'psychoneuroses', 'personality disorders' and 'addictions.' Some of these had already received psychoanalytic treatment for up to 6 years previously without significant improvement. Patients received LSD at doses increasing gradually from 25–150 μg, from 1–26 times, at intervals of 1–6 weeks. The authors report an improvement in 80% of patients and that in only three cases did LSD fail to facilitate psychotherapy. Unfortunately, the exact proportion of the 44 patients with 'psychoneuroses' that contribute to this total percentage remains unclear from the paper. The authors claim nonetheless that most patients in this subgroup showed some improvement. The authors conclude that compared with previous therapy without any drugs, 'With LSD therapy most patients showed greater depth of therapy and greater acceleration of therapy', and that, 'patients who would be unacceptable for analysis or almost any type of deep psychotherapy were benefited by LSD therapy' (Chandler and Hartman, 1960).

A very different therapeutic method is described by Maclean and colleagues in the treatment of 100 patients (61 alcoholics with poor prognosis and 39 patients with other psychiatric disorders) (Maclean et al., 1961). Instead of using the 'psycholytic' approach of repetitive lower doses of the drug, considerably larger doses of LSD ranging from 400–1500 μg were administered in a one-off session. This is known as the 'psychedelic' approach. A group technique was also used and generally a psychiatrist, psychologist, psychiatric nurse and music therapist were present for each therapy session. Utilizing this method, in a group of 25 patients suffering from 'anxiety' and 'depressive reaction neuroses', improvement was reported in 92% of patients.

Sherwood and colleagues describe the 'psychedelic' approach further where, 'an individual can have a single experience which is so profound and impressive that his life experience in the months and years that follow become a continuing growth process' (Sherwood et al., 1962). The authors report on 25 cases (marital problems, alcoholism, personality disorders and neuroses) in which simultaneous doses of LSD and mescaline were administered in an attempt to produce such unique experiences. Improvement was seen in 84% of the total cases but specifically four out of seven (57%) in the 'neuroses' group. It was felt the amount of improvement is correlated with the subject's willingness to face himself during the session, accept the material encountered and act upon it.

Another method of LSD treatment in neurotic disorders is described by Martin in which the therapist takes a more direct approach with the patient, sitting with them through most of the session, playing a different role for each patient according to their emotional needs (Martin, 1964). The author reports impressive results with their technique that combines both behaviouristic and psychoanalytic methods of therapy. Response was seen in

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95% (57 out of 60) of patients described as 'severe neurotics' receiving LSD analysis weekly for an average of 20 sessions. No information is provided as to the doses involved.

Further work on the use of LSD in the treatment of 'chronic neurotics' is described by Geert-Jörgensen et al. (1964). In a group of 129 patients who had not benefited from years of therapy before being treated with LSD they report a total improvement rate of 55%. For the purpose of this review, including only those patients described as 'anxiety neuroses', 'depressive neuroses' or 'endogenous depression' the percentage improvement increases to 68% (19 out of 28).

A shared theme throughout the studies described so far is the lack of any control group. Whitaker, an Australian psychiatrist, describes his findings in the use of LSD in psychotherapy in 100 patients (Whitaker, 1964). He explains the method of setting up a control group presented serious difficulty as 'The response of the first few patients was so encouraging that it was considered that it would be unfair to withhold LSD from apparently suitable patients in the interests of experimental design'. Instead a control group was selected from patients treated in recent years of a similar range of diagnoses and duration of illness. In the LSD group 47% of cases were successful, 18% were borderline successful and 35% were failures. This compares with the retrospectively collected control group in which only 12% of cases were successful, 30% were borderline successful and 58% were failures (Pearson's χ^2 test for significant differences between the control and LSD groups: $p = 4.03 \times 10^{-7}$). Focusing on those with 'depression,' treated with LSD psychotherapy, an improvement was reported in 17 out of 21 patients (81%).

Other groups have found similarly effective results using LSD in the treatment of depressive patient groups. Baker describes results in the treatment of 150 psychiatric patients over a 4-year period from 1961–1964 (Baker, 1967). Improvement was seen in 91% of 'depressive' cases (10 out of 11). Comparable results are described in a report by Leuner in another group of 11 patients with 'depressive reactions,' in which improvement was seen in 8 patients (73%) following LSD psychotherapy (Leuner, 1967).

The largest, most sustained and systematic studies of psychedelic drugs and psychotherapy to date were carried out at the Spring Grove State Hospital and the Maryland Psychiatric Research Center through the 1960s and early 1970s. Savage and colleagues report on work with a cohort of 'neurotics' and 'depressives' treated in an outpatient setting (Savage et al., 1966). Following a period of extensive preparation involving weekly interviews for 4–8 weeks, patients would undergo a single high-dose 'psychedelic' session. Patients were given 200–300 µg of LSD together with 200–300 mg Mescaline 'if necessary', spending the day in the company of a male and female therapist, listening to music or viewing visual stimuli such as family photographs. Instead of providing any direct interpretation, the therapists' role during the session was one of companionship and emotional support. This focus on a supportive rather than an active therapeutic role was based on the shared expectation between patient and therapist that the patient would have their own experience in which they would learn something about themselves that might prove useful in altering their life in a more self-fulfilling direction. Regular interviews in the period following the session provided the opportunity for analysis and integration of the patient's experience. The authors report improvement in 80% (62 out of 77) following an evaluation at 6 months. Later this team provided an analysis of a larger group of 243 patients that had been through the same program (Savage et al., 1967). Consistent improvement was seen in 81% of the total cohort (197 out of 243) and more specifically in 81% of patients with 'psychoneurotic depressive reactions' (29 out of 36).

The final study included in this review was carried out at the Spring Grove State Hospital investigating LSD-assisted psychotherapy in the treatment of inpatients with 'severe chronic neuroses' (Savage et al., 1973). After an initial psychiatric assessment, 96 patients were randomly assigned to a high-dose (350 µg) LSD group, a low-dose (50 µg) LSD control group and a conventional treatment group. Personality and behaviour measures (Minnesota Multiphasic Personality Inventory (MMPI), the Eysenck Personality Inventory, and the Personal Orientation Inventory) were administered before and 5–7 days after treatment. Significant treatment effects occurred in 19 out of 50 test variables indicating superiority of high-dose LSD treatment over conventional treatment. Although usually of a lower magnitude, low-dose LSD treatment was also found to be superior to conventional treatment with significant treatment effects in 11 of the 50 test variables.

Discussion

We have collated and summarized the pre-prohibition literature on the use of psychedelics in the treatment of broadly defined UMD in Table 1. A total of 21 studies published between 1949 and 1973 were included. LSD was, by far, the most commonly used psychedelic. Mescaline was occasionally used. The absence of psilocybin is discussed below. The sample size ranged from 5 to 77, with a total aggregated sample size of 423 across all the studies where this was clearly defined. The number of psychedelic sessions ranged from 1 to 58 and the therapeutic paradigms applied were variable. The dose of LSD used ranged from 20 to 1500 µg. Mescaline was used at doses of 200–400 mg, in combination with LSD. Many studies used titrated dosing schedules that took account of individual patient responses to the drug.

Savage et al. (1966) neatly summarized the methodological difficulties of these pre-prohibition papers.

> *'Nearly all studies have serious shortcomings…namely, 1) anecdotal evidence; 2) inadequate assessment procedures; 3) insufficient follow up; 4) naïve statistical treatment; 5) lack of controls.'*

We agree with these criticisms, noting also that a meta-analytical approach to the reported studies is impossible as continuous outcome measures were only collected by 1 research group. Only four studies have any mention of a control group (Savage, 1952; Savage et al., 1973; Sloane and Lovett Doust, 1954; Whitaker, 1964) and in only one (Savage et al., 1973) could the control group be deemed to be (A) adequately selected and (B) adequately described. Outcomes measures were generally so vague that the only meaningful grouping was a dichotomous variable reflecting those who were felt by their clinicians to have 'improved', as opposed to those that did not. Given the heterogeneity in definition, 'improvement' cannot be further defined. Clearly this is subject to bias and is neither systematic nor objective. In those studies where the number of patients who were

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deemed to have improved was actually specified (19 out of 21), 335 (79.2%) out of 423 patients were judged to have improved, ranging in the various studies from 40% to 95%. Studies using higher doses of psychedelics and/or combining psychedelics with psychotherapy or psychological support appear to show better results.

In an attempt to delineate more classical depressive disorders from the wider clinical definitions of 'anxiety' and 'neurotic' disorders subsumed within the review, we also repeated this analysis restricted to cases classified as 'depressives,' 'depressive reactions,' and 'depressive neuroses', where this was specified. Of the papers where there was sufficient information to do this (11 out of a total of 21 papers) improvement was seen in 73.7% (101/137). Further restricting the sample to purely 'depressives' and 'depressive reactions', improvement was seen in 72.5% (58/80). Data on those who were felt to have worsened with treatment was either incomplete, or not included at all. The degree of improvement is notable even if the presumption must be that it is biased in favour of a therapeutic effect. The research deserves repetition in a modern, controlled context.

In response to the Thalidomide tragedy, the US introduced the Kefauver–Harris Drug Efficacy Amendments in 1962, which required well-controlled trials to evidence a drug's efficacy and safety before it could be marketed (Peltzman, 1973). These changes heralded modern paradigms of trial design, which rely on randomisation of individuals to a placebo or active treatment, and blinding of both assessor and participants to the intervention. This is thought to partially compensate for selection, performance and detection bias and serves to isolate the effect of the drug from the confounds of its surroundings. However, there are inherent difficulties with such designs when psychotropic drugs are being used, and particularly with psychedelics (Oram, 2012), for four reasons.

First, blinding is largely impossible. Therapeutic doses of psychedelics induce subjective and objective changes in feeling, thinking and behaviour that are usually obvious both to recipient and observer. Second, and on this basis, placebo control is problematic because the absence of the psychedelic effect is also obvious. Thirdly, and perhaps most pertinently to psychedelic trials, the 'set' (psychological state) and 'setting' (interpersonal and physical environment) within which the drug is experienced are inextricably linked to the therapeutic effect (Grinspoon and Bakalar, 1997). Attempting to isolate the drug from these variables, as modern trials attempt to do, will miss the widely accepted point that the therapeutic effect is subsumed within, and inextricable from, the interaction between psychedelic, set and setting. Finally, and a point common to trials in mood disorders in general, the diagnostic and aetiological heterogeneity in patients diagnosed with UMD is famously wide. Some patients have broadly adaptive personalities with particular sensitivities to certain stressors. Others have chronic and enduring patterns of learned helplessness or other personality factors. Others may have biologically mediated mood problems derived from subclinical imbalances in immune or endocrine function. Most will have a variable mixture of these factors contributing to the clinical picture. Consequently, routine clinical treatments for UMDs are also variable, requiring a flexibility in clinical approach that modern trial designs are particularly designed to avoid.

Active placebos have been used to attempt to compensate for difficulties in blinding and placebo control. In a randomized, double blind trial using psilocybin in psychedelic-naïve volunteers over two or three sessions to investigate mystical experiences, clinicians were told that participants would receive at least one dose of psilocybin, but that at other sessions a variety of other drugs might be administered (Griffiths et al., 2006). They were then asked to guess the drugs used immediately after each session. In fact, only psilocybin or methylphenidate were used in the trial. A total of 23% of sessions were misclassified (that is, the clinician either thought a methylphenidate session was a psilocybin session or that a psilocybin session was something other than psilocybin). However, when clinicians did misclassify a session they tended to misclassify a methylphenidate session as a psilocybin session. Furthermore, when psilocybin was given but the clinician did not accurately guess this, most participants still reported deeply meaningful, mystical experiences. This suggests that the occurrence of a mystical experience is not likely to be an artefact simply of expectation or suggestion (Griffiths et al., 2006), and may suggest that the double-blind, active placebo condition is a more favourable trial design. Randomisation between low and high doses of psychedelic is also a credible design strategy given the difficulties described, a design that was partially implemented in a study in 1973 by Savage et al. included in this review (Savage et al., 1973). This showed statistically significant superiority of LSD at a dose of 350 μg when compared with conventional treatment over a wide range of psychological test variables in a sample of 96 patients with 'severe chronic neuroses' randomized to low-dose LSD, high-dose LSD and treatment as usual. Correction for multiple statistical comparisons was not performed.

Attempts to standardize the context, or setting, of the psychedelic experience are possible in controlled trials, but the number of variables implied by this and the pragmatics of controlling them, suggests that a significant degree of variation is unavoidable. Whilst the dose of drug and basic environmental context (the layout of the room, decoration, sound and ambience, for example) can be largely controlled in medical research settings, the psychotherapy itself must inevitably be flexible. Defined training programs in psychedelic research and psychotherapy are now being set up to provide some structure for this, such as the new 'Certificate in Psychedelic-Assisted Psychotherapies & Research' in California, which took its inaugural intake of students in 2015 (Denenmark, 2015). However, a raft of questions remain to be answered. In the pre-prohibition literature, distinction was made between 'psycholytic' therapy, which used low doses of psychedelics to facilitate access to unconscious material, and 'psychedelic' therapy, which used high doses to elicit therapeutic mystical/spiritual experiences. There is some evidence that mystical experiences with psilocybin are associated with increased well-being and personal meaning over a year later (Griffiths et al., 2008), however it is not known whether one paradigm is generally superior to the other, or whether there is variation in response according to disorder and paradigm used.

Carefully designed clinical trials that incorporate biological mechanism studies may help resolve some questions. For example, the dichotomy between the more verbal 'psycholytic' paradigm and the largely ineffable 'psychedelic' paradigm raises the question of whether they reflect a common continuum of response to psychedelics, or distinct entities in themselves. Modern neurobiology and neuroimaging studies may help answer this question, and ideally such appraisals of mechanism will need to be

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embedded within clinical efficacy trials. If the two paradigms appear mechanistically distinct in terms of neurobiology, it may suggest that the two paradigms will have different therapeutic efficacies in different disorders and, perhaps, different personality types. However, there should be robust ethical scrutiny and oversight of trial designs that expose clinical trial participants, who by definition will be psychiatrically unwell, to the emotional difficulties implicit in brain scanning and blood sampling. Hitherto, neuroimaging studies using psychedelics have been restricted to healthy volunteers.

In summary, it appears that a particularly careful and well-considered balance between the needs of the participants and the needs of the trial will be required in studies using psychedelics. Funders and research ethics committees will need to understand the inherent difficulties discussed above if they are to scrutinize trial designs using psychedelics successfully, and trial designers will need, similarly, to be detailed and explicit about the environmental and psychotherapeutic milieu in which a study is to be performed. Clinical trials using psychedelics will need to be sufficiently methodologically detailed at the point of publication to allow genuine replication. Scientific mechanism studies will need, ideally, to be pursued alongside clinical trials if this is pragmatic and ethical. Within this multi-pronged approach to evidence gathering, and a sufficient degree of definition, replicable results and common threads of insight into the nature and applicability of psychedelics to medicine in general, and to psychiatry in particular, should emerge with time.

Psilocybin was marketed under the trade name '*Indocybin*' by the same pharmaceutical company that marketed LSD (Sandoz). Whilst it was used in individual patients, this systematic review did not find any clinical trials of its pre-prohibition use in broadly defined mood disorder. This is likely to be because psilocybin (and its active metabolite, psilocin) were not isolated until 1959, and the drug marketed after this (Hofmann et al., 1959). By this time, LSD research was well underway and it is likely that most clinicians would have wanted to stick to what was an established pharmaceutical entity, rather than risk the potential complications of trying a new one. With this in mind, it is notable that psilocybin has been favoured over LSD in modern clinical trials. There are several possible reasons for this. First, psilocybin has a shorter duration of action than LSD or mescaline, which makes day-case treatment sessions feasible, without the need for supervised (and costly) overnight hospital stays. Second, anecdotal evidence from recreational users suggests that psilocybin is less liable to occasion highly distressing psychological reactions (although this may simply be because psilocybin is easier to measure than LSD). Finally, and perhaps most importantly, LSD remains a particularly stigmatized drug. Not only is this likely to colour individual experiences of the drug effect, but it is also likely that this stigma still negatively affects the chances of successful applications to grant funders and research ethics committees.

These observations lead naturally to a discussion about the risks of using psychedelic drugs in medical and recreational settings. Physiologically, psychedelics (particularly LSD and psilocybin) are notably safe. LSD and psilocybin have a toxicity ratio (estimated lethal dose as a ratio of the estimated therapeutic dose) of 1000 or more (alcohol, by comparison, has a toxicity ratio of about 10, cocaine about 15, ketamine about 38 and fluoxetine about 100) (Gable, 2004).

The risk of harm from recreational use of psychedelics should not be conflated with the risk of harm from medical use. Turning to recreational use first. In 2010, an analysis of harms to the end-user and society caused by a range of recreationally used psychoactive substances ranked LSD and psilocybin amongst the safest of all those studied (Nutt et al., 2010), however the precipitation of psychotic disorders by psychedelics remains a concern. Carhart-Harris and Nutt, in a web-based self-report questionnaire of recreational use of psychedelics, noted prolonged psychotic reactions were reported by 1.3% (6 of 463) of LSD users and 1.6% (8 of 503) of psilocybin users in their sample (Carhart-Harris and Nutt, 2010). However, this proportion included those reporting derealisation, which is generally classified as an anxiety derived phenomenon rather than a psychotic phenomenon. Despite this, the prevalence is not significantly greater than might be expected in the general population. Three large population studies have found that use of psychedelics is associated with a lower relative risk of suicide (Hendricks et al., 2015), need for psychiatric medication and psychological distress (Johansen and Krebs, 2015), and recidivism (Hendricks et al., 2014). Despite the authors attempting to correct for sociodemographic variables in these studies, it is still possible that these results are confounded by users of psychedelics tending not to be from such socially disadvantaged groups when compared to users of other recreationally used substances. Very rare, reports of recreational users committing apparent acts of suicide whilst under the influence of psychedelics do exist, and are unfortunately emphasized by media outlets (Keeler and Reifler, 1967; Reynolds and Jindrich, 1985).

Turning to harm in medical settings, Cohen noted a single case of prolonged (>48 hours) psychosis in a survey of 1200 research participants given psychedelics, and this case turned out to have an identical twin suffering with schizophrenia (Cohen, 1960). Savage et al. (1973) noted that of 'the nearly 500 diverse patients treated [with LSD]' only two cases of psychosis were noted. This first was in a 21-year-old patient with 'severe chronic neurosis' treated with 350 μg of LSD. This patient had a history of psychotic episodes in the past, and recovered with psychotherapy and antipsychotic medication. The second case was a 'schizoid subject' with a history of alcoholism, but no further details were given about the case. According to recent guidelines (Johnson et al., 2008), the first two of these participants would have been excluded from participation in modern trials, whilst it is impossible to tell whether the third would or would not have.

In the most comprehensive review of specific adverse reactions to psychedelics in medical and recreational settings, Strassman (1984) pointed out that researcher's and clinician's attitudes to psychedelics appeared to result in considerable variation in judgement about what was, and was not, considered a risk or an adverse event:

> *'It is important to use caution in discussing the concept of adverse reactions to psychedelic drugs. At one extreme are those who believe that the drug-induced state itself is either primarily a pathological one, i.e. a "model psychosis", or that the desire to induce such a state is a function of pre-existing personality dysfunction. At the other extreme is the view that even the most disorganized, frightened, dysfunctional, and regressed reactions to psychedelic drugs are necessary/healthy reactions seen in throwing off "straight" society's*

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"shackles" and in reaching a "higher" level of consciousness. The description and/or reporting of adverse reactions to psychedelics is, therefore, subject to some degree of investigators' perspective on the use of these drugs.'

As a natural extension of this, Strassman also points out, about LSD:

'One of the most confounding aspects of almost all studies of either acute or chronic effects of LSD is their lack of pre-LSD data. The role of LSD in producing "LSD psychoses," brain damage, long-lasting personality change, and flashbacks is difficult, if not impossible to discern without pre-LSD values for the dependent variables'

His conclusions about the adverse effects of LSD are summed up in the following paragraph:

'With the available data, it appears that the incidence of adverse reactions to psychedelic drugs is low when individuals, both normal volunteers and patients, are carefully screened and prepared, supervised and followed up, and given judicious doses of pharmaceutical quality drug. The few prospective studies noting adverse reactions have fairly consistently described characteristics predicting poor response to these drugs. The majority of studies of adverse reactions, retrospective in nature, have described a constellation of premorbid characteristics in individuals seeking treatment for these reactions where drugs of unknown purity were taken in unsupervised settings.'

Whilst such research certainly deserves repetition (particularly because modern research with psychedelics is tending to use psilocybin) a summation of the evidence suggests that the risks associated with medically controlled and supervised use of psychedelics are low and that evidence-based guidelines (Johnson et al., 2008) improve safety even further. In this context it is also notable that far more dangerous substances, such as opiates, are routinely used in medical therapy even though recreational use is also widespread, and certainly much more dangerous than recreational use of psychedelics. No deaths have been unambiguously linked to the physiological toxicity of classical serotonergic psychedelics whereas in 2014, in the US alone, 10,574 people died of street heroin overdoses, and a further 18,893 from prescription opiate overdoses (National Center for Health Statistics, 2015).

A single pilot study of psilocybin in the treatment of resistant MDD was recently completed in the United Kingdom (Carhart-Harris et al., 2016). In this open-label feasibility trial, 12 patients with treatment-resistant unipolar major depression received two oral doses of psilocybin (10 and 25 mg) 1 week apart, in a supportive setting, with psychological support and medical supervision before, during and after each session. Follow up was from 1 week to 3 months post treatment. 8 of 12 patients achieved complete remission of symptoms at 1 week and 7 patients (58%) continued to meet criteria for response (50% reduction in BDI score relative to baseline) at 3 months, with 5 of these still in complete remission. The therapy was well tolerated, with no serious adverse events.

The American psychologist and LSD researcher, Betty Eisner, summarised the psychotherapeutic mechanism by which LSD, and by implication other psychedelics, may work as follows (Eisner and Cohen, 1958):

(1) LSD lessens defensiveness;
(2) there is a heightened capacity to relive early experiences with accompanying release of feelings;
(3) therapist–patient relationships are enhanced;
(4) there is an increased appearance of unconscious material.

If the aetiology of UMD in some patients can be understood, at least in part, as the present day emotional and behavioural sequelae of unresolved traumas and emotional conflicts from the past, with anxieties about the future, it is reasonable to hypothesize that psychedelic psychotherapy will catalyse the resolution of such conflicts in a proportion of patients where other treatment modalities have failed.

There is a pressing economic need for such interventions. Unipolar depressive disorder costs the United States alone over US$210 billion annually (Greenberg et al., 2015). Response to treatment is often suboptimal and entrenched, maladaptive patterns of thought, feeling and behaviour are the hallmark of resistance to treatment. Whilst long, detailed forms of dynamic, analytical and behavioural psychotherapy may change such patterns over the course of years, they are expensive and time consuming. Psychedelic therapy may represent a form of catalysed psychotherapy whereby the drug acts to hasten the breakdown of habitual maladaptive templates of thinking and behaviour in supportive therapeutic environments. The evidence from the pre-prohibition literature, whilst unsystematic and methodologically suboptimal, suggests that this is worth re-investigating. Furthermore, a recent pilot study in treatment-resistant depressive disorder has shown encouraging results. Taken together, the evidence suggests that there is a strong medical and economic argument for the further investigation of psychedelics in the treatment of unipolar mood disorders in sensitively designed, modern clinical trials.

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