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Invited review

Psychiatry & the psychedelic drugs. Past, present & future

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ABSTRACT

The classical psychedelic drugs, including psilocybin, lysergic acid diethylamide and mescaline, were used extensively in psychiatry before they were placed in Schedule I of the UN Convention on Drugs in 1967. Experimentation and clinical trials undertaken prior to legal sanction suggest that they are not helpful for those with established psychotic disorders and should be avoided in those liable to develop them. However, those with so-called 'psychoneurotic' disorders sometimes benefited considerably from their tendency to 'loosen' otherwise fixed, maladaptive patterns of cognition and behaviour, particularly when given in a supportive, therapeutic setting. Pre-prohibition studies in this area were sub-optimal, although a recent systematic review in unipolar mood disorder and a meta-analysis in alcoholism have both suggested efficacy. The incidence of serious adverse events appears to be low. Since 2006, there have been several pilot trials and randomised controlled trials using psychedelics (mostly psilocybin) in various non-psychotic psychiatric disorders. These have provided encouraging results that provide initial evidence of safety and efficacy, however the regulatory and legal hurdles to licensing psychedelics as medicines are formidable. This paper summarises clinical trials using psychedelics pre and post prohibition, discusses the methodological challenges of performing good quality trials in this area and considers a strategic approach to the legal and regulatory barriers to licensing psychedelics as a treatment in mainstream psychiatry.

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1. Introduction

The classical psychedelic drugs include mescaline, psilocybin, dimethyltryptamine (DMT) and D-lysergic acid diethylamide (LSD). Coined by psychiatrist Humphrey Osmond in a letter he wrote to Aldous Huxley in 1956, the word 'psychedelic' is derived from the ancient Greek words *psychē* (ψυχή, translated as "soul" or "mind") and *dēlein* (δηλειν, translated as "to reveal" or "to manifest"). Therefore, psychedelic literally translates as 'mind manifesting' or 'soul revealing' (Osmond, 1957). Other terms such as 'hallucinogen' and 'psychotomimetic' are less favoured, perhaps because they place too much emphasis on individual elements of a multi-faceted subjective state.

Psychedelics were used long before the Western world was introduced to them in 1897, when Arthur Heffter isolated mescaline from the peyote cactus. The earliest direct evidence for use of psychotropic plants dates back 5700 years in the north eastern region of Mexico (Bruhn et al., 2002), where carbon-dated buttons of peyote cacti and red beans containing mescaline were found in caves used for human habitation. The Eleusian ceremonies of ancient Greece were likely based around some form of psychedelic compound (Wasson et al., 2008). Psilocybin containing 'magic' mushrooms, which grow all over the world, appear to have been used ubiquitously (Akers et al., 1992; Letcher, 2008). Mescaline is still used in Native American Church ceremonies (Stewart, 1987). In Brazil (McKenna et al., 1984) and the broader Amazonian basin (Schultes and Hofmann, 1979), ritual healing practices and spiritual ceremonies are practiced using *ayahuasca*, a drink which combines plant derived DMT and β-carboline monoamine oxidase inhibitors that allow it to be used orally.

The archetypal psychedelic in modern Western society, LSD, was first synthesised in 1938 by Albert Hofmann as part of a systematic investigation of compounds derived from the ergot alkaloids at the Sandoz laboratories in Switzerland (Hofmann, 2013). The ergot alkaloids, which include lysergic acid and its derivatives, were known to be responsible for episodes of mass poisoning in medieval Europe from stocks of grain spoiled with the parasitic fungus *Claviceps Purpurea*. In smaller doses, a specific ergot alkaloid (ergometrine) was also known to be effective for treating bleeding in women after childbirth due to its vaso- and utero-constrictive properties. LSD was the 25th derivative of lysergic acid that Hofmann synthesised, explaining why it is sometimes referred to as 'LSD-25' (Hofmann, 2013).

In animal testing, LSD was found to be physiologically unremarkable and the compound was shelved. Hofmann describes how he decided to resynthesize LSD in 1943 on the basis of a '*peculiar presentiment … that this* [compound] *might possess properties beyond those established in the first pharmacological studies*' (Hofmann, 2013). On April 16th of that year Hofmann accidentally contaminated himself with a small amount and, noticing some unusual psychic effects, purposefully ingested 250 mcg 3 days later, whereupon the full, and remarkably potent, effects of LSD on the psyche became apparent for the first time. Further investigation of LSD by Sandoz found that, despite its potency, it was a notably non-toxic compound physiologically. Recognising that its psychoactive properties were likely to be of interest both to psychiatrists and academics, it was marketed in 1947 under the trade name 'Delysid' and made freely available to those interested in researching its properties. Hofmann also isolated and synthesised the active component of psilocybe 'magic' mushrooms, psilocybin, in 1958 (Hofmann et al., 1959). This was marketed by Sandoz under the brand name 'Indocybin'.

At a time when psychiatry lacked effective medical therapies, the discovery of LSD was of interest, with some key features noted. Firstly, acute intoxication appeared to mimic some of the symptoms of acute psychosis, particularly ego-dissolution, thought disorder and visual misperceptions (although not, notably, auditory hallucinations). Secondly, there appeared to be an increased awareness of (and emotional connection to) repressed memories and other elements of the subconscious, which was thought to be potentially useful in those failing to make progress in psychotherapy. Physiological toxicity was not observed, even after very large overdose. However, initial testing of psychedelics in patients with schizophrenia showed that they were not helpful, exacerbating psychotic symptoms and failing to lead to clinical improvement. Trials in depressive, anxious, obsessive and addictive disorders were more encouraging, with the psychedelics noted to have therapeutic potential within psychologically supportive contexts (Eisner and Cohen, 1958) and a low risk of toxicity (Cohen, 1960). By the end of the 1960s, hundreds of papers described the use of mescaline, psilocybin and (most frequently) LSD in a wide variety of clinical populations with non-psychotic mental health problems (Grinspoon and Bakalar, 1981).

However, as the psychedelics diffused into wider society and recreational use increased, some individuals reported a variety of ongoing symptoms including visual distortions, flashbacks and other symptoms that occurred long after the drugs had left the body. This came to be classified as 'Hallucinogen Persisting Perceptual Disorder' (Halpern and Pope, 2003). Unethical and covert use of psychedelics along with a general hardening of socio-political attitudes towards drug use contributed to the decision to place psychedelics in Schedule I of the 1967 UN Convention on Drugs. Medical use ceased and research dwindled until the turn of the millennium, since when there has been a steady renaissance of clinical and academic interest in the psychedelic drugs, reflected by a socio-political narrative that has increasingly questioned the relative benefits and harms of the so-called 'war on drugs' (Godlee and Hurley, 2016; Hari, 2015).

This paper presents a synopsis of selected clinical studies with psychedelics performed before 1970 and all major clinical studies

since the turn of the millennium. We discuss the controversies and practical considerations in designing modern clinical trials with psychedelics and review the formidable legal and regulatory hurdles that must be overcome if psychedelics are to become licensed medicines in psychiatry again.

2. Pre-prohibition clinical studies

2.1. 1895–1940. Studies with mescaline

The first medical report of use of a classical psychedelic in Western medicine was made by Prentiss and Morgan in the United States in 1895, who reported the ceremonial use of buttons of the peyote cactus by indigenous people in Central America (Prentiss and Morgan, 1895). Mitchell, reporting in the British Medical Journal in 1896, reports self-experimentation with peyote, describing closed-eye visual experiences and commenting that '*for the psychologist this agent should have value*' (Mitchell, 1896). This was a view repeated by Havelock Ellis in 1897, describing the experience as '*… mainly a saturnalia of the specific senses, and chiefly an orgy of vision … it is of no little interest to the physiologist and psychologist*' (Ellis, 1897).

Whilst Arthur Heffter isolated the active component of peyote (mescaline) in 1897, there is limited further mention of it in the English medical literature until 1913, when Alwyn Knauer administered mescaline by subcutaneous injection to himself and other volunteering physicians (Knauer and Maloney, 1913). Knauer had worked as an assistant to the psychiatrist Emil Kraeplin who, aside from his involvement in the inception of psychiatric diagnosis, was also interested in the effects of psychoactive drugs in producing psychopathology. However, his experimentations were restricted, according to Knauer, to '*substances, which … produce mental states which have little similarity to actual insanities*'. Administering mescaline repeatedly both to themselves and other volunteering physicians, they commented, '*Soon after the onset of the visual hyperesthesia, to nearly all the investigated persons, out of total darkness, kaleidoscopic pictures appeared.*' Whilst commenting on the '*… vividness of the [visual] hallucinations … they came unsought, they were uncontrollable …* ' they also noticed that '*the independence of the hallucinations to thought and will was never quite absolute*. On the nature of the conscious experience under mescaline, they noted that it '*… remained practically unclouded … somewhat similar to … consciousness in hypnosis*' (Knauer and Maloney, 1913). Whilst the nature of hallucinations in psychosis remained opaque, Knauer and Maloney recognised that the mental state induced by mescaline bore some similarity to the psychotic state.

Heinrich Kluver, in 1926, again experimenting on himself, commented, in addition to the established visual imagery, on changes in 'object-awareness' and 'self-awareness' (referred to in the original German '*gegenstandsbewusstsein*' and '*ichbewusstsein*'):

> *'My body and its organs seemed to be most of the time non-existent or detached from me as a perfectly functioning machine. While speaking I seemed to listen to a speech apparatus … In general, the line of demarcation drawn between 'object' and 'subject' in normal state seemed to be changed. The body, the ego, became 'objective' in a certain way, and the objects became 'subjective'. They became subjective not only in the sense that they behaved as visionary phenomena, but also in the sense that they gained certain affective qualities … There is no doubt that these changes in 'Gegenstands- und Ichbewusstsein' are comparable to those observed in schizophrenia'*. (Kluver, 1926)

In 1936, Erich Guttman, then working at The Maudsley Hospital in London, United Kingdom, raised the possibility of a therapeutic effect of mescaline (Guttmann, 1936). He, and a variety of other colleagues, gave the drug to an undisclosed number of '*medical students*', '*undergraduates*', '*normals*', '*psychopathic patients*', '*manic-depressives*', '*schizophrenics*', '*depressives*', '*morphinists*' and those suffering from '*derealisation*' and '*depersonalisation*' phenomena (Guttmann, 1936). Not publishing any sort of objective results, he nonetheless made the first observation of the potential therapeutic utility of the mescaline-induced state in psychotherapy, noting:

> *'There is reason to suppose that patients in such a state may be very susceptible to psychotherapeutic influence … If it is so, the intoxication could be made use of as a sort of forced or concentrated analysis'*.

Similarly, he recognised the importance of the drug for psychiatrists attempting to understand …

> *' … the complicated interplay of aetiological factors in the origin of psychoses. Careful analysis of one intoxication like mescaline promises a reliable basis for knowledge in the field of toxic psychoses generally, and perhaps hints for the solution of the great problem of psychiatry, that of schizophrenia.'*

2.2. 1940–1970. Studies in psychotic disorders

Perhaps because mescaline was never marketed (it was first synthesised by Ernst Spaff in 1919 and then manufactured by the pharmaceutical company Merck as a research chemical), but perhaps also because of the predominance of psychoanalytic theory at the time, its use by psychiatrists was sporadic and infrequent. In contrast, after Hofmann synthesised LSD in 1943, not only did Sandoz provide it free of charge to psychiatrists, but it came at the same time as the emerging idea that psychiatric states might have biological, rather than psychological, aetiologies. Moreover, regulation of the medical community, and of medical research, was minimal. Growth of interest in LSD was rapid.

In 1950, Busch and Johnson (1950), working in Missouri, United States, published one of the first studies using LSD in patients. They gave 21 patients, mostly hospitalised with schizophrenic or manic episodes, LSD. They observed that all patients showed '*increases in activity*', particularly those with mania. Based on these observations they gave LSD to a further 8 patients. 3 had diagnoses of catatonic schizophrenia, 4 '*psychoneurosis*' and 1 '*psychosomatic*'. Describing the results narratively,

> *'The effect … disturbed the barrier of repression and permitted a re-examination of significant experiences of the past, which sometimes were lived with frightening realism. With this, some of the patients were then able to re-evaluate the emotional meaning of some of their symptoms, and improved. Most were better able to organize their ideas in relation to real rather than fancied problems and were seen to experience and express relevant emotion. Two of the patients [both psychoneurotic] … were improved sufficiently to discontinue treatment … '*

In a further group of 59 individuals with schizophrenia divided into 17 with *'pseudoneurotic'* schizophrenia, 26 with *'undeteriorated'* schizophrenia and 16 with *'deteriorated'* schizophrenia, Paul Hoch and colleagues variously administered LSD and mescaline (Hoch et al., 1952). Not recording any objective data, they commented that the drugs '*markedly aggravated*' the mental symptomatology of the individuals they studied. Those with 'deteriorated' schizophrenia showed '*catatonic withdrawals*' in response to the drugs.

Whilst noting the propensity of the drugs to uncover new material, the therapeutic value of the drugs in this patient group was considerably doubted. This was echoed in studies by Liddell (Liddell and Weil-Malherbe, 1953) and Pennes (Pennes, 1954), who observed worsening in those with undeteriorated and deteriorated forms of schizophrenia, but improvement in some with 'pseudoneurotic' forms of schizophrenia. 'Pseudoneurotic schizophrenia' is an archaic term that included a multitude of depressive, anxious and obsessive symptomatology. None of these reports include details of follow up.

Making some attempt at follow up, Herman Denber and Sydney Merlis gave 500 mg mescaline intravenously to 25 patients with schizophrenia. Whilst 1 patient achieved 'complete remission' from her symptoms (and was well at 1 year follow) and 3 patients showed temporary remission of symptoms, psychotic symptoms were either reactivated or worsened in the remainder (Denber and Merlis, 1955). In another study published in 1957, Sidney Merlis gave 24 patients with chronic schizophrenia between 500 and 750 mg of mescaline and noted that 1 '*improved sufficiently to be discharged*', 7 '*temporarily*' improved and in the remainder '*no change*' was noted (Merlis, 1957). Reporting of adverse events or those that worsened with treatment was not included in the report. He concluded that mescaline was not a clinically effective agent in schizophrenia.

After the early 1960s, clinical studies of the use of LSD and mescaline in psychosis rapidly diminished as it became clear that the drugs exacerbated the symptoms of most and did not lead to clinical improvement. However, the differences between the psychosis characterised by schizophrenia and the state characterised by LSD was still of interest. Langs, in 1968, published a detailed questionnaire study comparing schizophrenic patients and healthy controls who were randomly assigned to be given LSD or placebo (Langs and Barr, 1968). They noted that those with schizophrenia manifested '*somatic and persecutory delusions and hallucinations which qualitatively extended far beyond anything reported by our LSD subjects*'. Nonetheless, "*paranoid schizophrenics' responses resembled those of LSD-25 subjects in regard to feelings of unreality, loss of controls, changes in the meanings of experiences, and suspiciousness; they did not, however, exhibit the body image changes and elation-related effects found in many of the drug subjects*.' It was noted that the hallucinatory element of the LSD experience tended to be largely visual in nature, whereas in the schizophrenic state auditory hallucinations predominated.

2.3. 1940–1970. Studies in neurotic disorders

Ronald Sandison, then working at the Powick Mental Hospital near Worcester, United Kingdom, published a paper in 1954 in which 36 patients with predominantly '*psychoneurotic*' disorders were treated with variable doses of LSD given over a variable interval (usually weekly) in the context of psychotherapy (Sandison et al., 1954). LSD dosage was started at 25 mcg and then increased until an '*adequate*' reaction was observed. This paper described the '*psycholytic*' method of psychedelic psychotherapy: using LSD within the context of psychotherapy to '*loosen*' ego defences and catalyse access to traumatic material. 27 out of 30 with more classical neurotic and depressive disorders were reported to have benefited from the intervention, although this was a subjective judgement made by the treating clinician. There was no control group and no details of those patients who worsened with the treatment.

Reporting an extension of their research in a publication in 1957, Sandison reported 6 month follow up in 93 patients with *'severe neuroses'* (Sandison and Whitelaw, 1957). Of these 93 (of which 30 were also included in the original 1954 paper), 21 (22.6%) were 'recovered', 20 (21.5%) were 'greatly improved', 20 (21.5%) were 'moderately improved' and 32 (34.4%) 'not improved'. Again, there were no objective measurements, no control group and no information on those who worsened in this study.

Chandler and Hartman, working in California, published a work in 1960 in which 110 patients with predominantly '*psychoneurotic*' and '*personality disorder/trait*' diagnoses were given a total of 690 psychotherapy sessions using LSD, usually given in gradually escalating dosages between 50 mcg and 150 mcg (Chandler and Hartman, 1960). They also commented on the therapeutic utility of music in ' … *helping to bring out affectively charged memories and fantasies*'. Experiences under LSD were likened to '*a waking dream*' with the aim of therapy ' … *to understand it in terms of its emotional meaning rather than to worry about its objective validity*.' Of these 110 patients, 50 showed 'considerable', 'marked' or 'outstanding' improvement, 38 showed 'some' or 'slight' improvement and 22 showed 'little or no change' or were 'slightly worse'. No patients were judged to be 'definitely worse'. No control group was reported.

Attempting to provide a control group, Whitaker, working in Australia, described the use of an average of 3.28 LSD psychotherapy sessions in the treatment of 100 patients, comparing those treated with LSD psychotherapy to a group of patients treated in years previous to the study that were similar in terms of diagnosis and duration of illness (Whitaker, 1964a, 1964b). Of the 100 patients, 49 had 'psychoneuroses', 27 'personality disorder', 21 'sexual disorders' and 3 'residual schizophrenia'. Outcomes reported were clinician and patient agreements of improvement, divided into 'successful', 'borderline' and 'failure'. Of the 100 patients undergoing LSD therapy, 47 were judged to be successful outcomes, 18 borderline and 35 failure. In the control group 12 were judged to be successful, 30 borderline and 58 failures. The rate of success was observed to be higher (75%) in those with the shortest duration of illness (0–2 years) as compared to those with the longest (more than 21 years), where only 37% were classed as successes. Of those 35 who were deemed as treatment failures, 19 '*evaded*' ongoing therapy after their first LSD experience. None of the 3 residual schizophrenics were judged to have improved, however '*a successful result was obtained in more than half the cases of anxiety state, hypochondriasis, hysterical personality, antisocial character disorder, anorexia nervosa and exhibitionism*'. Outcome data was based on subjective judgements and the results were not analysed statistically.

Probably the largest studies of the therapeutic utility of psychedelics in the pre-prohibition era were carried out at the Spring Grove State Hospital and the Maryland Psychiatric Research Center, both in Baltimore, Maryland, United States during the 1960s and early 1970s. Reporting on a total of 243 patients with a variety of non-psychotic psychiatric diagnoses that included anxiety and depressive disorders, personality disturbances and alcohol addiction, Charles Savage and colleagues also pointed out '*the crucial importance of non-drug variables as determinants of reactions to chemical agents* [which is] *not confined to the psychedelics … '* (Savage et al., 1967). They administered LSD without the context of formal psychotherapy. LSD at a dose of 200–300 mcg was given, with mescaline at a dose of 200–400 mg given to potentiate the effect in some patients. Emotional support and companionship was provided by a male and female sitter, but with no attempt made at interpretation of material. Follow up was the next day, then at 1, 2, 4, 8, and 12 weeks and finally at 6 months. A questionnaire was then sent, retrospectively, to the first 113 patients in the sample. Ninety-three replied. 83% reported '*lasting benefit*' and this was found to be '*highly correlated (tetrachoric r = 0.91) with the report of a greater awareness of an ultimate reality*'. The claimed improvement rate was 76% at one to three months post LSD, and 85% in the

three to six months after LSD, this remaining constant after 12 months. Clinician ratings of improvement were made in retrospect by 4 raters, with improvement ratings divided into 'worse', 'none', 'some', 'substantial' and 'marked'. Of 243 patients, 197 (81.1%) were judged to have improved to some degree: 35.8% showing 'some' improvement, 26.3% showing 'substantial' improvement and 18.9% showing 'marked' improvement. Of the remainder, 16.9% showed no improvement and 2.1% were 'worse'.

2.4. 1940–1970. Studies with alcoholism

Clinical studies using LSD in the treatment of alcoholism before 1970 benefited from a more systematic approach than other disorders, probably because drinking behaviour is easier to quantify objectively. Several reasonable quality controlled studies were undertaken, particularly during the latter 1960s, however initial studies were usually uncontrolled. For example, Maclean and colleagues gave 61 alcoholics and 39 patients with other diagnoses 400–1,500 mcg LSD on an undisclosed number of occasions, following them up for up to 18 months (Maclean et al., 1961). Whilst noting that, of the alcoholics, 30 were 'much improved', 16 were 'improved' and in 15 there was 'no change', there was no comparison control group.

In another study that included a comparison group, Jensen gave LSD to 58 alcoholics on an inpatient unit in Ontario, Canada, comparing this to 35 alcoholics given group psychotherapy and 45 receiving 'standard' care from psychiatrists not connected to the study (Jensen, 1962). By chi square analysis, they reported a significant difference in rates of abstinence between those given LSD and those given group psychotherapy and standard care. However, the control groups were not matched and the authors stated that the group treated with LSD were composed of people who remained in follow up, whereas the control groups included those lost to follow up. The methods of statistical analysis, chi square statistic and p value for significance were also not stated.

More systematic studies were published after 1965, often with non-significant results. Smart et al., in 1966, reported the effect of a single LSD experience under controlled conditions on the behaviour of 30 alcoholics who were either inpatients or outpatients in Toronto, Canada (Smart et al., 1966). They were randomised to a control group that received standard care including psychotherapy, a group who received standard care plus a 60 mg dose of ephedrine sulphate (a drug chosen because it shares some similar subjective effects to LSD but with no known efficacy in alcoholism), and standard care plus an 800 mcg dose of LSD. Drug treatments were administered on a psychiatric ward, with participants kept overnight. Otherwise treatment was the same. Both participants and therapists were blind to treatment allocation. Nonetheless, in 19 out of the 20 drug sessions, the therapists correctly guessed the drug condition. Baseline and 6 month follow up alcohol usage data was collected in all groups by a participant- and researcher-rated questionnaire. Researchers following up participants at 6 months were blind to treatment and analyses were completed prior to blinding being broken. No significant differences were observed between the groups in terms of pragmatic measures of alcohol misuse.

Hollister et al., working in 1969 at the Veterans Administration Hospital in California, USA, reported the results of a controlled comparison of 72 male inpatients with alcoholism randomised to a single dose either of 600 mcg LSD or 60 mg of dextroamphetamine (Hollister et al., 1969). Music and low lighting was provided and a research assistant was available for reassurance, but no attempt at psychotherapy was made. Baseline and follow up measurements of drinking and associated social effects were recorded with a scale designed and validated for the trial. Follow up data was collected at 2, 6 and 12 months post treatment by a researcher blind to treatment and independent of the treatment programme. Of the 72 patients, 20 had dropped out at 2 month follow up (10 in each group) and 27 had dropped out of follow up by 6 months (11 in the LSD group and 16 in the dextroamphetamine group). In terms of mean change of questionnaire scores, analysed by ANOVA, those in the LSD group were significantly improved over the dextroamphetamine group ($F = 8.5$, $p < .01$), however the difference was not significant at 6 month follow up. Those who dropped out did not differ significantly in baseline scores compared to those who did not. At 12 month follow up, only 17 patients remained in the LSD group and 12 in the dextroamphetamine group, and the authors considered analysis of this group unproductive.

Ludwig et al., working at the Mendota State Hospital in Wisconsin, USA, published in 1969 a study in which 176 male inpatients with alcoholism were randomly allocated to one of three LSD treatments and a control condition (44 participants per group) (Ludwig et al., 1969). All participants allocated to the LSD groups received 3 mcg per kg of body weight, with the treatments differing by the nature of therapy offered during the LSD experience. One group received LSD plus hypnosis plus psychotherapy, a second group LSD plus psychotherapy and a third group LSD alone. The fourth 'control' group were required to spend an equivalent amount of time in the treatment room by themselves, but no intervention was otherwise given. Therapists were not blind to treatment group. Evaluation was with a variety of symptomatology, drinking behaviour and social adjustment inventories taken at baseline then immediately post-treatment and at 3, 6, 9 and 12 months after treatment. Researchers collecting follow up data were blind to treatment allocation. All groups showed consistent improvements and no significant difference was found between the LSD groups and the control groups. A similar approach, and non-significant result, was found in two further controlled studies by Bowen (Bowen et al., 1970) and Tomsovic (Tomsovic and Edwards, 1970), with borderline significant results found by Pahnke (Pahnke et al., 1970).

Meta-analysing the previous 6 studies, Krebs and Johansen found that LSD treatment was significantly associated with maintained abstinence at 1–3 months (OR = 2.07 95% CI, 1.26–3.42; $p = .004$), but by 6 months statistical significance was lost (OR, 1.42, 95% CI, 0.65–3.10, $p = .38$) (Krebs and Johansen, 2012).

3. Clinical trials prior to prohibition: discussion

Studies of the clinical utility of psychedelics published prior to 1970 were, like many studies of that time, methodologically suboptimal. A non-exhaustive list of the obvious problems includes the following:

1. Treatment groups were inadequately and inconsistently defined
2. Treatments were inconsistently applied amongst groups
3. Control groups were often absent
4. Attempts to blind study teams were usually absent
5. Outcome measures were not validated
6. Outcome data was inconsistently reported
7. Adverse outcomes were often not reported
8. Statistical analysis of results was often absent
9. Power calculations were not used to estimate sample sizes needed to detect an effect

Nonetheless, the pre-prohibition research strongly suggested that psychedelic drugs were not useful for those with established psychotic disorders and should probably be avoided in those liable to develop them. Worsening of psychotic symptomatology was observed in most of those with pre-existing schizophrenia and

whilst the occasional case was observed to recover, no trial reported improvements that might not otherwise have been attributable to the passage of time.

Reports were more encouraging in trials with so-called 'psychoneurotic' disorders, a term which covers a wide variety of anxious, obsessive and depressive states. We have systematically reviewed trials in broadly defined unipolar mood disorder in another work, which showed that nearly 80% of participants in these trials were judged to have 'improved' by their clinicians (Rucker et al., 2016). The data was not of sufficient quality to meta-analyse and clinical improvement was usually a subjective judgement, rarely based on objective or validated scales. Indeed, initial trials were usually little more than case series reported by clinicians who probably had positive expectations about treatment. Studies in later years suggest more moderate preconceptions, but still reported subjectively defined efficacy in many cases. However, in controlled trials with alcoholism using quantitative measures of alcohol use, borderline or non-significant findings were often reported. Given the lack of power calculations, this may reflect a lack of power to detect an effect or a true lack of efficacy. Krebs and Johansen's meta-analysis of these studies suggests the former, at least in the use of LSD in the treatment of alcohol dependent individuals (Krebs and Johansen, 2012).

Side effects, or adverse events, during the experience were generally not reported systematically, if at all. Interpretation of an adverse event's aetiology varied according to research team, particularly for mental phenomena. This ranged from a directly toxic action of the drug on the brain, which tended to cluster within studies of those with schizophrenia, to the expected expression of repressed trauma, which tended to cluster within studies of those with neuroses and alcoholism. This may reflect both the varying perspectives of cliniciansabout the aetiology of mental disorder and the pharmacological effect of the drugs. We have listed reported adverse events (non-exhaustively in view of space) in Table 1. Immediate adverse events were more often reported than delayed adverse events. In no particular order (frequencies were rarely reported), headaches, palpitations, gastrointestinal disturbances, changes in temperature perception, feelings of tremulousness or dizziness, and a variety of other somatic complaints were most commonly reported.

A consistent theme was a disparity between the degree of subjectively reported physical symptoms and objective clinical signs on medical examination, which tended to reveal only minor increases in pulse rate and blood pressure along with pupillary dilatation and, occasionally, signs of body temperature changes (shivering and piloerection, or sweating). The significance of this disparity is uncertain, however may represent both an increased subjective awareness of bodily sensations under the influence of psychedelics, as well as drug induced changes in the autonomic nervous system itself.

Sidney Cohen, in 1960, attempted to systematically investigate the incidence of adverse events during treatment with psychedelics by sending a questionnaire to 62 investigators who were using LSD or mescaline in healthy subjects or patients (Cohen, 1960). 44 investigators replied. The data covered almost 5000 individuals given LSD or mescaline on a total of more than 25,000 occasions. No instance of physiological toxicity was reported. Of those with pre-existing psychiatric problems receiving LSD or mescaline, the rate of attempted suicide was 0.12%, completed suicide, 0.04% and psychotic reactions lasting over 48 h, 0.18%. The rate in healthy subjects was 0%, 0% and 0.08% respectively. No instance of addiction was reported. The instances of these serious events appear rather low and the study can be criticised for relying on the recall of clinicians who may have underestimated (or been unaware of) the nature and degree of adverse reactions in their subjects, particularly in those lost to follow up (who may have been at higher risk of experiencing them).

In a narrative report of nine cases who had suffered a variety of persistent psychotic and neurotic symptoms after recreational use of, or medical treatment with, LSD, Cohen and Ditman concluded that complications were '*much more likely to occur after the unsupervised or inexpert use of the drug.*' Whilst the study was unsystematic, the majority of cases occurred using illicit LSD taken within a psychologically destabilising milieu that also included other psychoactive drugs and lack of access to timely medical assistance (Cohen and Ditman, 1963). This was a view echoed by Strassman in a comprehensive review of adverse events to psychedelics in 1984 (Strassman, 1984).

As recreational use of LSD and mescaline increased in the 1960s, so evidence of toxic psychological reactions in sensitive individuals accumulated, with occasional tragic cases (Keeler and Reifler, 1967) accompanied by sensationalist media reporting. This paralleled investigation of psychedelics as so-called 'truth drugs' or chemical weapons, particularly by the Central Intelligence Agency (Lee and Shlain, 2007). An immoral failure, these experiments (and the public outcry over them) accompanied a more general hardening of socio-political attitudes towards psychoactive drugs. Moreover, unethical medical use of psychedelics probably occurred in some centres. Whilst documentation is patchy, concerns about this issue were reflected in a legal ruling in Denmark, where the 'LSD Damages Law' was enacted in 1986. This led to a series of 151 patients gaining compensation in the 1980s and 1990s for a variety of psychiatric symptomatology that was presumed (but not proven) to have resulted from LSD treatment that was claimed sometimes to have been given under coercion, or without informed consent (Larsen, 2016). A critique of the report of these cases has recently been published (Erritzoe and Richards, 2017).

In summary, the research conducted prior to 1970 suggests that whilst there was certainly clinical interest in the therapeutic potential of psychedelics in patient populations with non-psychotic mental health problems, a firm conclusion about efficacy and safety was not reached prior to legal sanction that was largely socio-political in motivation, although also reflected medical concerns about the sequelae of recreational use. It is within this agnosticism and strict regulatory framework that the modern resurgence of research interest has taken place and to which we now turn.

4. Modern clinical studies

In 1967, psychedelics, including mescaline, psilocybin and LSD, were classified under Schedule I of the 1967 UN Convention on Drugs. This legally defined them as having no accepted medical use and the maximum potential for harm and dependence. Successive national legislation throughout the Western world tended to mimic the 1967 UN Schedules. Medical use of psychedelics ceased quickly because doctors were no longer permitted to prescribe them. Without a clinical focus, research dwindled almost to a standstill in the late 1980s and 1990s. This is depicted graphically in Fig. 1, which shows the annual number of publications listed in the database PubMed where the title refers to a classical psychedelic drug, expressed as a proportion of all PubMed publications, from 1950 to 2016.

The herald to modern clinical research using psychedelics were three papers investigating the effects of mescaline, dimethyltryptamine and psilocybin in healthy volunteers by, respectively, Leo Hermle et al. in Germany (Hermle et al., 1998), Rick Strassman et al. in the United States (Strassman and Qualls, 1994), and Franz Vollenweider et al. in Switzerland (Vollenweider, 1997). These studies formed the basis for a resurgence of further studies in healthy

Table 1
Summary of included studies, sorted by diagnostic category and year of publication. Lists of adverse events includes salient negatives. PR = pulse rate. BP = blood pressure.

Author(s)	Year	Predominant Diagnosis	Sample Population	Control Population	Drug/Dosage	Efficacy	Outcomes	Adverse Events (Immediate)	Adverse Events (Delayed)
Maclean et al.	1961	Alcoholism	61 Alcoholism 11 Personality disturbance 26 Neurosis 2 Psychosis	None	LSD 400–1,500 mcg	Yes	52 'much improved' 29 'improved' 19 'no change'	Frequency not stated. 'Transient nausea', 'mild headache', 'mild gastric distress'.	Not reported
Jensen	1962	Alcoholism	58 Alcoholism	35 Alcoholism - group therapy alone 45 controls - 'care' from other psychiatrists	LSD 200 mcg	Yes	Significant improvement in rates of abstinence for alcoholics receiving LSD over those receiving group therapy or standard care (chi square)	Frequency not stated. 'Anxiety', 'nausea', 'tension', 'headaches', 'side effects … are indicative of emotional conflicts'	4/58 (6.9%) treated with LSD were lost to follow up 18/35 (51.4%) treated with group therapy alone were lost to follow up 23/45 (51.1%) treated by other psychiatrists were lost to follow up.
Smart et al.	1966	Alcoholism	10 alcoholism	10 + 10 Alcoholism	10 - standard care 10 - standard care plus 60 mg ephedrine 10 - standard care plus 800 mcg LSD	No	No significant difference between groups	Not reported	Not reported
Hollister et al.	1969	Alcoholism	36 alcoholism	32 alcoholism	32 - LSD 600 mcg 32 - 60 mg dextroamphetamine	Yes	Superiority of LSD at 2 months. No significant differences at 6 months.	2 'nausea', 2 'vomiting', 2 'sufficiently agitated to require IM admin. of chlorpromazine 50 mg', 1 'grand mal seizure … in a patient with previous history of "rum fits"', 1 'moderate confusion requiring hospitalisation for 4 days'	10 (LSD) vs 17 (D'amphetamine) drop outs in each group at 6 months 1 suicide (group not stated)
Ludwig et al.	1969	Alcoholism	132 alcoholism	44 alcoholism	44 - standard care 44 - LSD 3 mcg/kg 44 - LSD 3 mcg/kg + psychotherapy 44 - LSD 3 mcg/kg + psychotherapy + hypnosis	No	No significant difference between groups	2 'LSD sessions had to be terminated'	Not reported
Bogenschultz et al.	2015	Alcoholism	10 Alcohol dependence	None	Psilocybin 300 mcg/kg or 400 mcg/kg	Yes	Significant effect on the percentage of heavy drinking days relative baseline	Mild elevation of BP 1 vomiting, 1 diarrhea, 1 insomnia	1 dropped out after first treatment
Osorio et al.	2015	Depression	6 Recurrent depressive disorder	None	Ayahuasca 2.2 ml/kg containing 0.8 mg/ml DMT & 0.21 mg/ml harmine	Yes	Significant reductions in depressive symptoms at 1 day, 1 week & 3 weeks.	3 vomiting. Frequency not reported: irritability, decreased insight	Not reported
Carhart-Harris et al. (b)	2017	Depression	20 Treatment resistant major depressive disorder	None	Psilocybin 10 mg & 25 mg	Yes	Significant effects on self-rated mood, maximal at 5 weeks.	1 'patient became uncommunicative' during the drug effect (duration not stated) 15 'transient anxiety lasting for minutes' 5 'transient nausea' 3 'transient paranoia'	8 'headaches lasting no longer than 1–2 days' No 'flashbacks or persisting perceptual changes' 5 'sought and successfully obtained psilocybin between 3 & 6 months [after treatment]'
Sanches et al.	2016	Depression	17 Recurrent depressive disorder	None	Ayahuasca 2.2 ml/kg containing 0.8 mg/ml DMT & 0.21 mg/ml harmine	Yes	Significant reductions in depressive symptoms up to 3	47% vomiting	Not reported

Table 1 (*continued*)

Author(s)	Year	Predominant Diagnosis	Sample Population	Control Population	Drug/Dosage	Efficacy	Outcomes	Adverse Events (Immediate)	Adverse Events (Delayed)
							week study end point.		
Grob et al.	2011	Life threatening disease	12 Anxiety/ adjustment disorder secondary to an advanced cancer diagnosis	Subjects act as their own control (randomised crossover)	Psilocybin 200 mcg/kg & Niacin 250 mg (control)	No	No significant difference between groups (positive trends observed)	Mild elevation of HR and diastolic BP	'No adverse psychological reactions from the treatment'
Gasser et al.	2014	Life threatening disease	12 Anxiety disorder secondary to an advanced cancer diagnosis	Unblinded crossover	LSD 200 mcg & LSD 20 mcg (control)	Yes	Significant reductions in state (not trait) anxiety at 2 months, sustained for 12 months	18 reports of adverse events in LSD group vs. 8 in active placebo group	6 reports of mild adverse events persisting until the next day No 'lasting psychotic or perceptional disorders'
Ross et al.	2016	Life threatening disease	29 Cancer related anxiety and depression	Blinded crossover	Psilocybin 300 mcg/kg & Niacin 250 mg (control)	Yes	Immediate, substantial and sustained clinical benefits (statistically significant). Variety of outcome measures.	Statistically significant increases in BP/PR 28% 'headaches/ migraines' 14% 'nausea' 17% 'transient anxiety' 7% 'transient psychotic-like symptoms'	No 'participants abused or became addicted to psilocybin' No 'cases of prolonged psychosis or hallucinogen persisting perception disorder' No 'participants required psychiatric hospitalisation'
Griffiths et al.	2016	Life threatening disease	51 Life threatening cancer with anxiety and depression	Blinded crossover	Psilocybin 22mg/70 kg or 30mg/ 70 kg & Psilocybin 1mg/70 kg or 3mg/ 70 kg	Yes	Statistically significant superiority of high dose vs low dose psilocybin	34% systolic BP > 160 mmHg (high dose) 13% diastolic BP > 100 mmHg (high dose) 15% 'nausea or vomiting' 21% 'physical discomfort (of any type) (high dose) 32% 'psychological discomfort (of any type) (high dose) 26% 'anxiety' (high dose) 1 'headache' 1 'transient paranoid ideation' (high dose)	No 'cases of hallucinogen persisting perception disorder or prolonged psychosis' 2/11 'delayed moderate headache after this high dose session'
Sandison et al.	1954	Neurosis	9 Obsessional 21 Depression/ Anxiety 4 Conversion hysteria 2 Other	None	LSD 25-400 mcg over 2–40 weekly sessions	Yes	4/9 Obsessional recovered/ improved 18/21 Depression/ anxiety recovered/ improved 3/4 Conversion hysteria recovered/ improved 2/2 Other recovered/ improved	Not reported	Not reported
Sandison & Whitelaw	1957	Neurosis	93 Predominantly neurotic (Includes 30	None	LSD 50-200 mcg	Yes	21 'recovered' 20 'greatly improved' 20 'moderately	Suicidal ideation, self harm, 'anxiety'	'Repetition of the acute phase of the experience days or weeks after treatment'

(*continued on next page*)

Table 1 (*continued*)

Author(s)	Year	Predominant Diagnosis	Sample Population	Control Population	Drug/Dosage	Efficacy	Outcomes	Adverse Events (Immediate)	Adverse Events (Delayed)
			from 1954 paper)				improved' 32 'not improved'		
Chandler & Hartman	1960	Neurosis	44 Psychoneurosis 36 Personality disorder/trait disturbance 22 Sociopathic disorder 8 Miscellaneous/ Other	None	LSD 50-150 mcg	Yes	4 'Outstanding improvement' 20 'Marked improvement' 26 'Considerable improvement' 23 'Some improvement' 15 'Slight improvement' 19 'Little or no change' 3 'Slightly worse' 0 'Definitely worse'	Not reported	1 suicide (previous history of attempts). 1 transient psychosis (1 day).
Whitaker (b)	1964	Neurosis	49 psychoneurosis 27 personality disorder 21 sexual disorder 3 residual schizophrenia	100 patients treated in previous years similar in terms of 'diagnosis and duration of illness'	LSD 100-250 mcg given 3.28 times on average. Total of 328 treatments given.	Yes	LSD/Control 47/12 'successful' 18/30 'borderline' 35/58 'failure' No statistical comparison performed	Rescue medication given in 14/328 (4.3%) of treatments because of 'uncontrollable acting out or intolerable distress'. 'Several refused further treatment because they found the experience too distressing'	1/328 (0.3%) 'recurrence of the LSD effect on the following day' 'In about 1/3 of cases there was transient increased distress between sessions' No instance of delayed psychosis No instance of drug seeking behaviour
Savage et al.	1967	Neurosis	63 psychoneurotic 2 schizophrenic reaction 117 personality disturbance 9 sexual deviation 24 alcohol addiction 27 other mostly adjustment reaction	None	LSD 200-300 mcg + Mescaline 200–400 mg 'if necessary' on one occasion	Yes	46 'marked improvement' 64 'substantial improvement' 87 'some improvement' 41 'no improvement' 5 'worse'	Not reported	1 'manic attack … treated successfully with psychotherapy' 1 'transient psychotic episode 5 months after LSD triggered by an alcoholic bender' 1 'claimed he had been harmed mentally'
Moreno et al.	2006	OCD	9 Obsessive compulsive disorder	None	Psilocybin 25 mcg/kg, 100 mcg/ kg, 200 mcg/kg & 300 mcg/kg	No	Significant main effect of time on YBOCS scores. No significant effect of dose.	1 transient hypertension (mild) 2 dropped out after session 1 'due to discomfort with hospitalisation'	Not reported
Busch & Johnson	1950	Psychosis	20 Schizophrenia 3 Mania 4 Psychoneurosis 1 Psychosomatic 1 Paranoid state	None	LSD. Dose not stated. Probably between 20 and 60 mcg	No	Nil objective results reported 'Improvement' in 2 psychoneurotic patients No improvement in schizophrenia patients	In order of frequency (numbers not stated): 'Gastric distress', 'nausea & vomiting', 'muscle irritability', 'dizziness', 'pupil dilation', 'hallucinatory flashes of light', 'chilliness', 'increase in pulse rate', 'headache', 'flushing of the skin'	Not reported
Hoch et al.	1951	Psychosis	17 Pseudoneurotic schizophrenia 26 Undeteriorated schizophrenia 16 Deteriorated schizophrenia	None	Mescaline 400–600 mg LSD 10-100 mcg	No	Nil objective results reported 4 'mild' deterioration 1 'marked' deteriorating 1 'severe' deterioration 'Catatonic withdrawls' in deteriorated	Frequency not stated. 'Increased anxiety', 'hostility', 'paranoid manifestations', 'visual hallucinations', 'slurred speech', 'chilliness', 'headache', 'trembling', 'flushing', 'numbness', 'sense of heat', 'hyperacusis',	Not reported

Table 1 (*continued*)

Author(s)	Year	Predominant Diagnosis	Sample Population	Control Population	Drug/Dosage	Efficacy	Outcomes	Adverse Events (Immediate)	Adverse Events (Delayed)
							schizophrenia group	'pupillary dilatations', 'nausea & vomiting', 'reinforces schizophrenic symptomatology & magnifies it'.	
Liddell & Weil-Malherbe	1953	Psychosis	3 Depression 4 Paranoid schizophrenia 9 Other forms of schizophrenia 2 Anxiety hysteria 3 Psychopathic states	None	25-60 mcg LSD 40-60 mg D-methylamphetamine	No	None objective Worsening of psychosis in those with schizophrenia 'Mood swings' with 'predominant euphoria' noted with LSD	Frequency not stated. 'Flushing', exacerbation of schizophrenic symptoms, 'mood swings', 'shivering', 'piloerection', 'agitation', 'terror', 'worsening of depression', somatic complaints	Not reported
Pennes	1954	Psychosis	20 Pseudoneurotic schizophrenia 25 Undeteriorated schizophrenia 10 Deteriorated schizophrenia	None	Mescaline unknown dose LSD 10-120 mcg	No	'Normalisation' reactions in 0% 'Intensification' reactions in 100% given mescaline and 64% with LSD	Frequency not stated. 'Anxiety & tension', 'hostility', 'paranoid manifestations', 'depression', 'hypochondriasis', 'phobias', 'somatic delusions', 'silliness', 'mannerisms', 'stereotypies', 'hysterical manifestaiotns', 'inferiority feelings', 'catatonic withdrawals'	Not reported
Denber & Merlis	1955	Psychosis	25 Schizophrenia	None	Mescaline 500 mg IV	No	1 'complete remission' 3 'temporary remission' 21 'psychosis reactivated or worsened'	Frequency not stated. 'Nausea', 'wretching', 'vomiting', 'sweating', 'palpitations', 'chest & neck pains', 'dyspnea', 'anxiety', 'restlessness', 'panic', 'visual hallucinations', 'auditory hallcinations', 'paranoid delusions', 'somatic delusions', 'acute catatonic withdrawal'	Not reported
Merlis	1957	Psychosis	24 Chronic schizophrenia	None	Mescaline 500–750 mg	No	1 'sufficient improvement for discharge' 7 'temporarily improved' 16 'no change'	7 'anxiety', 'increased activity', 'intensification of hallucinations & delusional thinking'	Not reported
Johnson et al.	2014	Tobacco addiction	15 Tobacco addiction	None	Psilocybin 20mg/70 kg or 30 mg/kg	Yes	Significant reductions in self-reported daily smoking from intake to 6-month follow-up	10/42 (23.8%) sessions included strong or extreme feelings of 'fear, fear of insanity or feeling trapped' Mild increases in BP/HR	8/10 participants reported transient, mild post psilocybin headache responsive to simple analgesia No increases in objective bothersome visual effects at 6 months

volunteers focussing on neuroimaging (Carhart-Harris et al., 2012, 2016b; Daumann et al., 2010; Muthukumaraswamy et al., 2013; Palhano-Fontes et al., 2015; Preller et al., 2017; Riba et al., 2004, 2006; Vollenweider, 1997), psychopharmacological (Kometer et al., 2012; Preller et al., 2017; Valle et al., 2016; Vollenweider et al., 1998) and neuropsychological (Carter et al., 2007; Gouzoulis-Mayfrank et al., 2005) correlates of the psychedelic state. This literature is beyond the scope of this clinically focussed review.

The first modern clinical trial investigating the safety and feasibility of using a psychedelic drug in a psychiatric patient population was published by Francisco Moreno and colleagues, working at the University of Arizona in the United States (Moreno

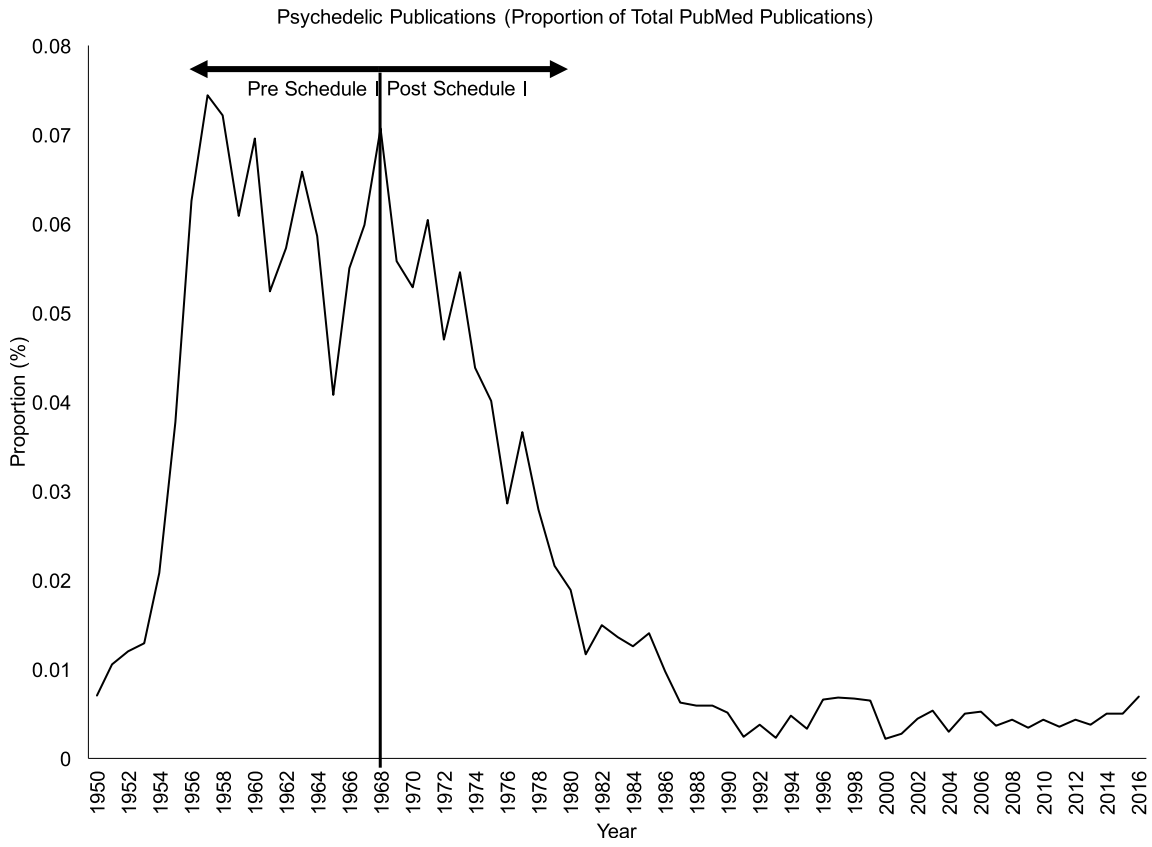


Fig. 1. The effect of Schedule I on psychedelic drug research. Number of PubMed publications in which a classical psychedelic drug is found in the title expressed as a proportion of all PubMed publications, by year, from 1950 to 2016.

et al., 2006). Nine subjects with treatment resistant obsessive compulsive disorder and no other major psychiatric pathology were given up to 4 different doses (25, 100, 200, 300 mcg/kg body weight) of psilocybin in an open-label design. Treatments were separated by at least 1 week. 29 doses were given in total. The Yale Brown Obsessive Compulsive Scale, the Hallucinogen Rating Scale and a visual analogue scale measuring overall symptomatology was administered at 0, 4, 8 and 24 h post dosing. Whilst significant reductions in OCD symptoms were observed in all dosing conditions, there was no significant difference between the different dosages of psilocybin, although the trial was likely underpowered to detect an effect. No serious adverse events were reported.

Matthew Johnson and colleagues, working at the Johns Hopkins University in Maryland, United States, published an open-label pilot trial in 2014 using moderate (20mg/70 kg) and high (30mg/70 kg) doses of psilocybin given to 15 otherwise psychiatrically healthy subjects with tobacco addiction undergoing a structured 15-week smoking cessation treatment (Johnson et al., 2014). Psilocybin was given at weeks 5, 7, and 13. Initial psilocybin dosing was with the moderate dose and the higher dose offered, but not enforced, in the subsequent sessions. A total of 19 meetings took place as part of the smoking-cessation programme and psilocybin delivery. Biological markers of smoking cessation were assessed at baseline, weekly throughout the treatment intervention and at 6 monthly follow up. A total of 42 psilocybin sessions were delivered. No clinically significant adverse events were reported during the treatment or follow up. 12 of 15 (80%) of participants were abstinent from tobacco as measured by biological markers at 6 month follow up. Whilst this was highly significant when pre and post treatment self-reported smoking figures were compared statistically, the authors were measured in their interpretations given the open label design and low numbers of participants.

In a further open-label pilot study in 2015 on addiction, this time to alcohol, Michael Bogenschultz and colleagues at the University of New Mexico, United States, gave psilocybin to 10 alcohol dependent patients (4 women) in addition to standard motivational enhancement therapy (Bogenschutz et al., 2015). Psychological support was given before, during and after 2 psilocybin sessions, spaced 4 weeks apart. The total treatment intervention was 12 weeks. Outcome data was collected at baseline and for 36 weeks in total. The dose of psilocybin used was either 0.3 mg/kg or 0.4 mg/kg. The primary outcome was the percentage of days spent drinking heavily compared between measures taken at baseline and weeks 5–12. 9 participants completed follow up. Results suggested, in line with studies in the 1960s using LSD in alcoholics, that the acute effects of psilocybin were less strong in this group. Large and statistically significant improvements in drinking behaviour immediately after treatment were seen and these correlated with the intensity of the drug effect. However, the open-label, uncontrolled design suggests caution is needed in extrapolating the finding. No serious adverse events were noted. Again, the authors concluded that psilocybin was a safe and feasible treatment to deliver in a clinical trial setting.

Three pilot studies using psychedelics in major depressive disorder have been published to date in the modern literature (Carhart-Harris et al., 2017, 2016a; Osório et al., 2015; Sanches et al., 2016). Our own open-label pilot study gave 2 doses of psilocybin (a 10 mg “test” dose and a 25 mg therapeutic dose) 1 week apart with psychological support before and after the experience to 20 patients with treatment resistant depression who were moderately to

severely depressed, but without psychotic features (Carhart-Harris et al., 2017, 2016a). Participants were withdrawn from their antidepressant medications prior to psilocybin treatment. The primary outcome measure was the mean change in the participant-rated quick inventory of depressive symptoms rating scale from baseline to 1 week after the second psilocybin treatment. Follow up was for 6 months. No serious adverse events occurred. Significant improvements in depression ratings were seen at 1, 2, 3 and 5 weeks, and at 3 and 6 month follow up. The maximal effect was seen at 5 weeks (Cohen's d = 2.3). Further treatment seeking by participants after 5 weeks, and particularly after 3 months, likely confounded follow up data collected at 3 and 6 months. 5 of the 20 participants sought and obtained psilocybin again during the follow up period. The trial established feasibility in this patient group and initial evidence of safety, but efficacy interpretations are precluded by the open-label, uncontrolled design.

Flavia de Lima Osorio and colleagues (Osório et al., 2015) and Rafael Sanches and colleagues (Sanches et al., 2016), both working in Sao Paulo, Brazil, reported studies where a single dose of ayahuasca to patients with recurrent depression. In Osorio's pilot study, 6 medication and ayahuasca naive participants (4 women) were given 2.2 ml/kg of a standardised preparation of ayahuasca containing 0.8 mg/ml DMT and 0.21 mg/ml of harmine. Measurement of depressive symptoms was with the clinician rated Hamilton Depression Rating Scale (HAMD) and the Montgomery Asperg Depression Rating Scale (MADRAS). Baseline measurements were compared with measurements taken at 1 day, 1 week, 2 weeks and 3 weeks after treatment. Significant reductions in depressive symptoms were seen at 1 day, 1 week, 3 weeks but not 2 weeks after treatment, both with the HAMD and MADRAS. The treatment was administered safely without any serious adverse events. Sanches and colleagues conducted a follow up to this work with an open-label study on 17 patients with recurrent depressive disorder given the same dose of ayahuasca, with identical outcome measures. Again, significant reductions in depressive symptoms were observed up to the three-week end point of follow up. The treatment was well tolerated with no serious adverse events. The failure to collect participant rated scales of depressive symptoms and the open-label design precludes clinical interpretation beyond feasibility and safety.

Finally, four separate studies have been published on the use of psychedelics in end-of-life anxiety associated with life threatening illness (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Charles Grob and colleagues, working in California, United States, gave 12 subjects (11 women) a moderate (0.2 mg/kg) dose of psilocybin and an active placebo (niacin 250 mg) several weeks apart with psychological support in a double-blind design in which subjects acted as their own control (Grob et al., 2011). All subjects had advanced cancer diagnoses and DSM-IV defined acute stress disorder, generalised anxiety disorder, or adjustment disorder with anxiety because of the cancer diagnosis. Four subjects were psychedelic naive. All 12 completed 3 month follow up. Non-statistically significant trends towards improvements in mood were observed. The treatment was well tolerated with no serious adverse events.

Peter Gasser and colleagues, working in Switzerland, gave LSD to 12 patients with anxiety associated with life threatening disease in a double-blind, randomised, active placebo controlled pilot trial (Gasser et al., 2014) with a 12 month qualitative follow up study also reported (Gasser et al., 2015). Drug free psychotherapy sessions were supplemented by two LSD assisted psychotherapy sessions given 2–3 weeks apart, in which participants were randomised to receive either 200 mcg or 20 mcg of LSD. An open label extension was offered to those randomised to the 20 mcg dose. The State Trait Anxiety Inventory was used as the outcome measure. Significant reductions were found in state, but not trait, anxiety at 2 months, sustained at 12 months. The treatment was delivered safely with no serious adverse events. This is the only modern trial to our knowledge that has used LSD in patients.

Two larger, double blind, randomised, placebo-controlled crossover trials investigating the efficacy of psilocybin in the treatment of anxiety and depression in patients with life-threatening cancer diagnoses were published from two separate groups in the United States in 2016 (Griffiths et al., 2016; Ross et al., 2016).

Working in New York University, Stephen Ross and colleagues gave 29 patients a single dose of 0.3 mg/kg psilocybin or 250 mg niacin, both in conjunction with psychotherapy. Crossover occurred at seven weeks. 2 therapists worked with each patient and extensive psychological support and therapy was provided. A variety of clinician and participant rated measures, including the State Trait Anxiety Inventory and the Beck Depression Inventory, served as primary outcome measures and were collected at 1 day prior to the first dose, 1 day, 2 weeks, 6 weeks and 7 weeks after the first dose, then 1 day, 6 weeks and 26 weeks after dose 2. The treatment was delivered safely, with no reports of serious adverse events. The group receiving psilocybin showed '*immediate, substantial, and sustained*' clinical benefits as measured by both clinician and participant rated scales that lasted for the 7 weeks prior to crossover and were also sustained at the final point of the study, 26 weeks after dose 2 (approximately 8 months after dosing). The group that received niacin as dose 1 showed transient reductions that were not sustained at 7 weeks. After crossover and receiving psilocybin, immediate and sustained reductions in anxiety and depression were observed, with the effect sustained at follow up at 6 and a half months.

Working in Baltimore, Roland Griffiths and colleagues gave psilocybin using a similar double blind, randomised, crossover design to 51 patients with life threatening cancer and associated anxiety and depressive symptoms (Griffiths et al., 2016). In this study, the placebo condition was a very low dose of psilocybin (1 mg or 3mg/70 kg) compared with a high treatment dose of psilocybin (22 mg or 30mg/70 kg) administered in a counterbalanced sequence with 5 weeks between sessions and 6 month follow up. Thus, those who received the low dose of psilocybin first received the high dose second and vice versa. Extensive psychological support was provided before, during and after the experience and the average length of participation in the study was approximately 9 months. The primary outcome measures were the Hamilton Depression Rating Scale and the Hamilton Anxiety Scale, two clinician-administered scales. The results showed statistically significant superiority of the high dose versus the low dose in terms of the primary outcome measures and self-reported measures when data at 5 weeks was considered. There were no serious adverse events reported. Because participants crossed over from low to high dose, and vice versa, at 5 weeks, the blind was effectively broken at this point. Significant associations between mystical type experiences and enduring positive changes were observed, reflecting previous research done by this group (Griffiths et al., 2008, 2006).

Commentary on both studies pointed out that the crossover design and degree of psychotherapy provided around the psilocybin experience may have confounded the effect attributed to psilocybin (Sellers and Leiderman, 2017). As ever, trials such as these are often subject to the so-called 'winner's curse', whereby effect sizes tend to be inflated in pioneering trials of new treatments due to a variety of subtle effects. Future trials are likely to report more modest findings.

5. Pathways to licensing: modern clinical trials & regulatory frameworks

Clinical trials with investigational medicinal products (IMPs) ultimately have one aim: to provide objective data to determine whether the IMP in question is safe and efficacious enough to justify a license. In the modern context of research with classical psychedelics, the IMP most likely to be licensed is psilocybin. However, the legal, regulatory and commercial hurdles to this are formidable. For the remainder of this article we concentrate on this process and discuss, within the context of modern trials so far, a strategic approach to tackling this challenge.

A license for an IMP results from approval from national medicine's regulatory bodies. In the UK, for example, this is the Medicines and Healthcare products Regulatory Agency. A license can be gained via various 'routes'. For example, existing drugs may be relicensed with market exclusivity for rare diseases to drive development in areas that would otherwise be commercially non-viable (the 'orphan' drug route). However, most drugs are developed de-novo for more common diseases based on the commercial potential predicated on a limited period of market exclusivity after licensing. Regardless of the route, licensing is based on objective data about the IMP's safety and efficacy in defined patient groups. This requires a series of randomised, controlled trials (RCTs) conducted on sufficient numbers of participants in a regulated fashion that seeks to collect valid, objective data about adverse outcomes and to disambiguate the effects of the IMP from other influences on outcome. A licensing decision is made based on a balanced judgement of the risks and costs of treatment with the IMP weighed against the risks and costs of the disease itself.

In the modern era, trials are divided into phases 1, 2, 3 and 4. Phase 1 trials are open-label and investigate safety in small numbers of healthy human volunteers. Phase 2 trials investigate safety and feasibility in modest numbers of patients. Whilst publications that result from phase 2 trials often report data about efficacy they are actually more concerned with safety and feasibility. They may be open label or controlled and the data is used to design phase 3 trials, which are are usually RCTs that investigate safety and efficacy in larger numbers of patients. Data from phase 3 trials often form the mainstay of evidence used for licensing decisions. Phase 4 trials are conducted on very large numbers of patients after a medicine has been approved and marketed and are designed to pick up treatment effects and rare side effects that could not reasonably be detected in phase 3 trials. At the time of writing, psilocybin is undergoing phase 2 trials, with phase 3 trials in the late stages of planning. This leads us naturally to a discussion about the safety of psilocybin and the feasibility of the clinical trials with it.

5.1. Safety

To date, 146 patients with a variety of psychiatric problems have been treated with psilocybin and reported in the modern medical literature. There have been no serious adverse events reported in these trials, although the infrequent reports of drop outs suggest absence of complete follow up data. A serious adverse event is defined as a reaction that results in death, is life threatening, results in prolonged hospitalisation or persistent or significant disability. The absence of this so far is consistent with research using psilocybin in healthy volunteers (Studerus et al., 2011), pre-prohibition research with LSD and mescaline (Cohen, 1960), modern population level data on recreational use of psilocybin mushrooms and other psychedelics (Carhart-Harris and Nutt, 2013; Hendricks et al., 2014, 2015; Johansen and Krebs, 2015; Krebs and Johansen, 2013a; Nutt et al., 2010; Walsh et al., 2016) and toxicology work (Gable, 2004). However, modern trials with psilocybin are notable for not collecting adverse event data systematically in a manner that allows aggregated analyses. The incidence of adverse events, and particularly any cases of hallucinogen persisting perception disorder, mania, psychosis, self-harm or suicidal behaviour will need to be compared between treatment and control groups, along with assessments about causality. A single consolidated database of adverse event information is necessary for regulatory approval. A number of groups have recently collaborated in Europe to establish this for trials using psilocybin in treatment resistant depression.

We have collated the most common immediate and delayed adverse events reported in the literature in Table 1. Transient anxiety, nausea, vomiting and mild increases in blood pressure and heart rate are the most frequently observed immediate adverse events. Headache is the most common delayed adverse event. No cases of prolonged psychosis or hallucinogen persisting perception disorder have been reported in modern trials with psilocybin, ayahuasca or LSD. Dropout rates have been low, however in these early trials participants may be a self-selecting group with favourable attitudes towards psychedelics, which may be reflected by the proportion reporting previous use. In our trial of psilocybin in treatment resistant depression 35% of participants had a lifetime history of psilocybin mushroom use. This is less than a recent worldwide survey of 22,289 recreational drug users, which found a lifetime prevalence of use of 43.1% (Winstock et al., 2013) but more than prevalence figures of 17% for lifetime LSD, mescaline or psilocybin use amongst 21–64 year olds in the 2010 US National Survey on Drug Use and Health (Krebs and Johansen, 2013b).

5.2. Dependence and diversion

There is very limited evidence that psychedelics cause dependence or addiction (Brunton et al., 2011; Morgenstern et al., 1994). Euphoria is not a consistent feature of the psychedelic experience, tolerance develops quickly and completely and there is no known withdrawal syndrome (Buckholtz et al., 1985; Cholden et al., 1955; Isbell et al., 1956). Psychological dependence appears to be rare, however research in this area is limited (Blacker et al., 1968). Thus psychedelics appear to have a low potential for abuse relative to other psychoactive drugs (Fábregas et al., 2010; Gable, 2007). Given the above and the fact that psilocybin would be delivered within a controlled healthcare setting rather than the community, the risk of diversion of drug supplies in the context of existing security measures for other controlled drugs used in healthcare settings appears to be low.

5.3. Feasibility and validity of RCTs with psychedelics

The ascendency of the RCT, which inherently attempts to separate drug effects from their contexts, has its origins in the Kefauver Harris Drug Amendments of 1962, which were developed in response to the thalidomide tragedy. However, a common theme in the literature is the opinion that psychedelics are therapeutic within a psychologically supportive context, rather than therapeutic per se. Given the disparity between the mechanism of action of psychedelics and the purpose of RCTs, some have argued that RCTs with psychedelics are fundamentally flawed and therefore not feasible (Oram, 2012).

To exemplify, modern RCTs with psilocybin have shown large effect sizes in distress associated with life threatening disease (Griffiths et al., 2016; Ross et al., 2016), however in these studies the psychological support provided was extensive. Criticism of these trials reflects this (Sellers and Leiderman, 2017). At the other extreme, Smart et al., in their 1966 study of LSD in alcoholism, tied their participants to a bed with a Posey belt and gave them a very

large dose of LSD (800 mcg) before attempting to engage them in a 3-way interview about their alcohol use (Smart et al., 1966). Perhaps unsurprisingly (the study was also probably underpowered) negative results were reported. A meta-analysis of pre-prohibition trials in alcoholism showed significant evidence of efficacy overall (Krebs and Johansen, 2012), however only one pilot study has been completed so far in the modern era using psilocybin in alcoholism. This found an encouraging effect on drinking behaviour, however again psilocybin was given in the context of quite extensive psychological support and a motivational enhancement programme (Bogenschutz et al., 2015).

It appears that the problem of determining the relative contribution of psychedelic and its context to the putative therapeutic effect is difficult. However, given that it would be unethical to give psychedelics without some sort of psychological and emotional support it seems germane to emphasise that this basic milieu is (and morally must be) the treatment being tested. Thus, trials that attempt to understand how different contexts interact favourably, or unfavourably, with psychedelics may be of more value than those that attempt to artificially separate them. At the same time, the evidence for a licensing decision must include trials that focus primarily on the drug itself.

Overall, whilst the RCT design is not ideal we conclude that carefully designed clinical trials with psychedelics are feasible and, since it would be unethical not to include a modest degree of psychological support within the design, RCTs with this are, by definition, valid. This has been demonstrated practically by modern pilot trials and RCTs with psychedelics, although the nature and extent of psychological support provided will attract differing opinions. We remain agnostic about outcome when the RCT design is applied in phase 3 trials of psychedelics, but agnosticism is ultimately why the research is necessary.

5.4. Commercial viability

Phase 2 trials are relatively inexpensive in comparison to phase 3 trials, which often cost many millions of dollars and thus generally require profit-driven commercial investment. This usually requires the commercial potential inherent from a period of patented market exclusivity for the developer. This allows recuperation of development costs and generates income that drives further work. However, since the patent on psilocybin (and LSD) has long expired, commercial viability, at first glance, seems doubtful. Treating psilocybin as an orphan drug is not an obvious solution to this because the proposed disease areas (such as treatment resistant depression) are not rare enough to fulfil criteria for this route. Trial costs are exacerbated further by the security and bureaucratic requirements imposed by Schedule I of the UN Convention on Drugs (Nutt et al., 2013). How can phase 3 trials with psilocybin be funded if there is no commercial potential to incentivise that funding?

The answer to this is multi-faceted. Recently, a UK based company announced a multi-center phase 3 trial of psilocybin in 300 patients with treatment resistant depression in Europe, with significant financial backing from investors, suggesting that the commercial potential does exist, at least in principle ("COMPASS - Navigating Mental Health Pathways," 2017). Grant holders in Europe and the US have started to fund trials with Schedule I substances over the last 10 years, perhaps reflecting a subtle shift in socio-political attitudes. Psychedelics tend to capture the imagination of the public (as well as the media) and significant sums have been raised through social media-linked crowd funding as well as from charitable and entrepreneurial sources (Emerson et al., 2014; Nichols, 2014). So, whilst the commercial potential in psilocybin may be somewhat atypically predicated, there is accumulating evidence that it now exists in sufficient quantity to fund the trials needed to collect evidence to submit to regulators.

5.5. Schedule I

With commercial potential, the practical and bureaucratic burdens imposed by Schedule I are inconvenient, but not insurmountable. Special licenses are required to process and administer Schedule I drugs and strict security protocols are necessary that require particular infrastructure. For example, pharmacies holding Schedule I drugs in the UK must be monitored by closed circuit television at all times and subject themselves to regular inspections. Storage containers holding Schedule I drugs must satisfy certain security standards and be securely fastened to reinforced walls or floors.

Those teams and institutions that have already conducted trials with psilocybin have implemented these requirements and are thus in a good position to conduct further research. With precedent comes familiarity and then replication. As the socio-political landscape changes, so do the attitudes of grant funders. In combination, this should stimulate other research groups to engage with the practicalities of this fledgling field of research, where there is, after all, plenty of room for expansion.

Moreover, there is historical precedent of Schedule I drugs being developed for medical use. Dronabinol (synthetic delta-9-tetrahydrocannabinol) was approved as an orphan drug for AIDS-related anorexia in 1985 and is now also approved for cancer chemotherapy related nausea and vomiting (Brafford May and Glode, 2016). Xyrem (sodium γ-hydroxybutyrate) was approved for the treatment of cataplexy associated with narcolepsy in 2004 (Owen, 2008). An extract of cannabis sativa (nabiximols) was licensed in 2010 in the UK for spasticity in Multiple Sclerosis (Lakhan and Rowland, 2009). Extracts of cannabis are also being investigated for certain forms of childhood epilepsy (Hussain et al., 2015). Generally, the drug development pipeline is similar and a successful licensing application results in the specific formulation of the drug being legally rescheduled. At this point, the drug becomes prescribable by medical doctors without the need for a special license, breaking the 'vicious cycle' of Schedule I research suppression (Nutt et al., 2013). With the force of commercial interest behind it, we anticipate a similar process for psilocybin if efficacy and safety are confirmed.

5.6. Patient groups

If trials using psychedelics are commercially and legally viable, then which patient groups should be focussed on? In a costs-driven world, it is likely that this will be those associated with high socio-economic burden, morbidity and mortality and where effective treatments are lacking or burdensome. Within psychiatry, the most logical initial focus is probably unipolar depressive disorder, with treatment resistant depression a priority. Unipolar depressive disorder is increasingly prevalent (Lopez and Murray, 1998; Murray and Lopez, 1997; "World Health Organisation," 2017), confers startlingly high socio-economic burden (Greenberg et al., 2015, 1993; McCrone et al., 2008; van Wijngaarden et al., 2004; Wang et al., 2003), is under-researched relative to disease burden, related to poorer outcomes in a wide variety of physical health problems (Moussavi et al., 2007) and is associated with a 20 fold increased risk of completed suicide (Harris and Barraclough, 1997). Of those who have a depressive episode, 85% will go on to have another and successive episodes increase the risk still further (Mueller et al., 1999). Treatment resistance, defined as failure to respond to at least two antidepressants, is common and longer term, depth psychological and social therapies are sufficiently expensive to deliver to make psilocybin therapy a viable potential

alternative, if safety and efficacy is demonstrated.

Whilst the initial focus of commercially driven trials is likely to be treatment resistant depression, the largest modern trials to date have been in psychological distress associated with terminal illnesses. Clinical scenarios involving the use of psychedelics in palliative care have inherent advantages in the process of gaining regulatory approval, because the safety data requirements are not as burdensome in groups where life expectancy is limited. Nonetheless, evidence of efficacy is still required and it is not yet clear where the funding for phase 3 trials of psilocybin in end of life care will come from.

Given the mechanism of action of psychedelics, the potential scope of application could be wide. Functional neurological disorders (Bryson et al., 2017) and anorexia nervosa appear interesting candidates for further exploration, for example. However, it is anathema to give psychedelics without informed consent, a point that leads us into a final brief discussion of the practical aspects of conducting trials with psychedelics such as psilocybin.

5.7. Practical considerations in clinical trials with psychedelics

Whilst their physiological safety is relatively well established, psychedelics elicit acute sensitivity to context and psychologically toxic reactions do occur. Rarely, tragic circumstances have occurred (Keeler and Reifler, 1967; Reynolds and Jindrich, 1985), often attracting disproportionate media coverage. In the light of this, what practical steps can be taken to minimise risks in psychedelic trials? A full discussion of this question has been covered elsewhere (Johnson et al., 2008), but we present some key points, revolving around our experience of using psilocybin in treatment resistant depression.

5.7.1. Recruitment

Recruitment in trials of psychiatric disorders is inherently difficult as the disorders themselves affect motivation and adherence. In addition to this more general problem, psychedelics are stigmatised. This combination may lead to selection bias. This can be overcome in part by using established clinical databases of patients that have consented to research contact, for example our own at King's College London (Perera et al., 2009; Stewart et al., 2009). This allows researchers to approach potential participants, rather than relying on a self-selecting sample of volunteers contacting the research team. On the other hand, self-selecting volunteers may be less liable to experience adverse events to psychedelics because of the positive preconceptions that motivate them to volunteer. Post hoc comparisons of study samples with case registers can also help determine to what extent study samples may differ to the populations they are drawn from, as well as allowing comparisons with 'treatment as usual' cohorts.

5.7.2. Screening

Clinical trials with psychedelics should include adequate procedures to screen out high risk individuals. A personal or family history of psychosis, personal history of mania, personal history of repeated violence towards others and a recent personal history of suicide attempt serious enough to require hospitalisation are sensible exclusions, as is current drug or alcohol abuse (unless this is the target for intervention). Medical screening should exclude those with serious neurological, renal, liver or cardiac disease. Given psilocybin's tendency to modestly increase blood pressure, uncontrolled hypertension should also be an exclusion. Women who are pregnant, at risk of becoming pregnant (inadequate contraception) or breast feeding should also be excluded. All participants should be registered with a local general or family practitioner and consent to the sharing of their records with the study team. Failure to consent to this should raise clinical suspicion about motivations for participation.

5.7.3. Concomitant medications

Commonly prescribed psychiatric medications should be withdrawn prior to use of psychedelics. Sufficient washout time is necessary, particularly for fluoxetine (Burke et al., 2000). Some tricyclic antidepressants, lithium, and the acute administration of selective serotonergic reuptake inhibitors (SSRIs) may increase sensitivity to psychedelics (Bonson and Murphy, 1996), as may haloperidol (Vollenweider et al., 1998). Chronic administration of SSRIs (Bonson, 1996; Stolz et al., 1983; Strassman, 1992) and monoamine oxidase inhibitors (Bonson and Murphy, 1996) appear to reduce sensitivity to psychedelics. Antagonists of the 5-HT2A receptor (mirtazapine and most antipsychotic drugs) attenuate response to psychedelics, as do benzodiazepines, particularly in acute use. The effect of antiepileptic drugs is not known.

5.7.4. Psychiatric & psychological support

A psychiatrist with an appropriate Schedule I license is required to prescribe and administer the psilocybin, manage other medication, medically monitor the treatment and provide assessment and management of mental state and risk during the participant's journey through the trial. At least one session of psychological preparation is required for all participants and is probably most effectively delivered by psychotherapists, psychologists or counsellors that have experience of the psychedelic state and appropriate training (Phelps, 2017). Likely effects of the psychedelic should be discussed and attention given to the possibility of long forgotten, unknown or emotionally charged material surfacing.

On the day of the treatment, participants should be accompanied at all times, preferably by those who provided psychological preparation. Onset with psilocybin starts at about 30 min, peaks after about 90 min and subsides after 4–6 h, making day case treatment viable. A comfortable, supportive environment with easy access to the lavatory is recommended. Music is often used to accompany the experience and has been shown to enhance the emotional response to psychedelics (Kaelen et al., 2015, 2016). A psychiatrist should be available at short notice, but need not necessarily be present.

Dysphoria, confusion, anxiety, agitation, panic and paranoia are all expected reactions in a proportion of psychedelic experiences. They are usually mild and respond to simple reassurance and attendance to physical pain or discomfort. Rescue medications are a last resort, given under the supervision of the psychiatrist. A short-acting benzodiazepine such as lorazepam or midazolam is recommended. If rescue medications are used, it may be necessary to arrange overnight stay and monitoring in the hospital or clinical research facility. Otherwise, participants can leave the research facility accompanied by a friend or relative once the clinical team is satisfied that this is safe.

Follow up of participants should include at least one session of psychological support with the therapist that has accompanied the participant through the trial. The question of 'how much is enough' is difficult. In a world where cost-efficiency is prioritised by most healthcare providers and given the requirements of regulatory bodies, we suggest that support should be minimal. We acknowledge that some may strongly disagree with this idea, but believe it strikes the right balance between idealism and pragmatism in the context of clinical trials. The trial itself will be a support if it includes regular follow up for collection of outcome measure data and psychiatric monitoring.

5.7.5. Blinding

In common with many trials of psychoactive drugs, effective

blinding of psychedelic therapy is hard to achieve because the subjective effect is often obvious to participants and observers. This creates expectancy effects in both trial participants and researchers that can bias outcome measures and inflate effect sizes. This suggests certain elements of trial design.

Firstly, ratings of primary outcome measures should be taken by trained raters who are blind to treatment allocation and preferably independent of the trial. Ratings should focus simply on the clinical state over the time period required for the rating and should not enquire about the nature and extent of the psychedelic experience. Videos of such ratings allow quality control, comparisons between raters and calculation of inter-rater reliability scores. Secondly, active placebos should be considered. Active placebos can be subthreshold doses of the investigational drug or a different drug with a similar (but non-therapeutic) psychoactive effect. Subthreshold dosages of the investigational drug have the advantage of simplicity and may be particularly effective if participants are not told the different dosing regimens in a trial (although this approach may raise ethical issues). However, subthreshold dosages may still be psychoactive, potentially reducing statistical power and increasing the likelihood of a type II error during analysis. Use of other psychoactive drugs as active placebos, such as methylphenidate, a benzodiazepine, or niacin, has been performed. However, this introduces the difficulty of choosing a drug that has a similar subjective effect but is known **not** to have a therapeutic effect. Crossover trials have been performed, but these are practically difficult and create problems with statistical analysis because of the putatively extended therapeutic effect of psychedelics. There is little consensus on which strategy is preferred.

6. Conclusions

Psychedelics have a long history of use and yet they attract emotive and often polarised opinions in modern Western society. History suggests they may have a place in the treatment of refractory neurotic disorders, particularly depressive disorder, anxiety disorders, addictions and in the psychological challenges associated with death and dying. Psychedelics appear to have a context-dependent effect. This mandates carefully designed trials within safe and comfortable settings staffed with psychotherapists and psychiatrists familiar with their use.

Whilst modern pilot studies (largely using psilocybin) have shown promise, treatments with classical psychedelics will need to stand up to the scrutiny of the RCT design, which itself poses significant challenges. The money to finance RCTs with psychedelics will likely come from a mixture of profit-driven commercial enterprises, charitable organisations, crowd-funding and government. The aim of RCTs is to demonstrate safety and efficacy. If safety and efficacy is confirmed, licensing and rescheduling will likely follow. At this point, psychedelics will need to demonstrate deliverability and cost-effectiveness if they are to become established and accepted treatments. Many treatments fail these tests. Delivery of psychedelics in real-world healthcare is likely to be expensive relative to other interventions, underlining our opinion that they are best investigated as options for those with socioeconomically costly psychiatric problems (such as treatment resistant depression) that are refractory to cheaper and more established therapies.

Author agreement/declaration

JR wrote the article with contributions from JI. DN reviewed and commented on the article. All authors have seen and approved the final version of the manuscript before submission.

Declaration of interests

JR has no conflicts of interest to declare. JI has no conflicts of interest to declare. DN has no conflicts of interest to declare.

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