Historic psychedelic drug trials and the treatment of anxiety disorders

Neil M. Weston1,2 | Damian Gibbs1 | Catherine I. V. Bird1 | Aster Daniel3 | Luke A. Jelen1,2 | Gemma Knight1,2 | David Goldsmith1 | Allan H. Young1,2 | James J. Rucker1,2

1Centre for Affective Disorders, The Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
2South London and Maudsley NHS Foundation Trust, London, UK
3Clinical Research Facility, King's College Hospital, London, UK

Correspondence
Neil M. Weston, Centre for Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, 16 De Crespigny Park, Denmark Hill, SE5 8AF London.
Email: neil.weston@kcl.ac.uk

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Abstract

Introduction: In this paper, we systematically review literature from 1940 to 2000 relating to the combined use of psychological therapies and psychedelic drugs in the treatment of ICD-10 anxiety disorders.

Methods: The databases Ovid MEDLINE(R), PsycINFO, and Multidisciplinary Association for Psychedelic Studies (MAPS) were searched for case reports and trials involving humans in the treatment of ICD-10 anxiety and related disorders. Twenty-four studies are described; four describe anxiety symptoms in diverse patient groups, 14 studies describe historic diagnoses that usefully correspond with ICD-10 anxiety disorders, six studies pooled results or failed to detail results specific to contemporary ICD-10 anxiety disorders. Two of the 24 studies reported are individual case reports while two of them were inadequate in terms of the reporting of outcome measures. Thus 20 studies were ultimately included in the summary analysis.

Results: Three of the 20 studies reviewed described improvements in anxiety by standardized measures ($p < .05$) and two studies found that this effect was dose related. Of the 20 studies included in the final analysis, 94 of 145 (65%) cases of “psychoneurotic anxiety reaction” as defined by Diagnostic and Statistical Manual of Mental Disorders-I showed improvement that ranged from moderate improvement to full recovery. Despite methodological inadequacies, the results from previous studies are encouraging and should be used to guide and inform further investigation.

Conclusion: The majority of studies indicate that a combination of psychedelic drug administration and psychological therapy was most beneficial. We found no study suggesting that the pharmacological action of psychedelic drugs in isolation is sufficient.

KEYWORDS
anxiety, LSD, psilocybin, psychedelics
1 | INTRODUCTION

The classical psychedelics comprise three main chemical classes: organic tryptamines (psilocybin and dimethyltryptamine [DMT] with ayahuasca being the combination of DMT and a monoamine oxidase inhibitor), the phenethylamines (mescaline), and the semisynthetic ergolines (lysergic acid diethylamide [LSD]; Geyer, Nichols, & Vollenweider, 2009). It is now accepted that the prototypic "psychedelic experience" arises from agonism at the serotonin 2A receptor subtype (HT2AR; Madsen et al., 2019; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998).

In the last decade, results from a number of studies on the safety and therapeutic potential of psychedelics hold significant promise for a range of conditions, including anxiety disorders. Recent, well-designed studies exploring the safety of these substances suggest that psychedelics may impact on depressive symptoms as well as anxiety associated with life-threatening diseases (Carhart-Harris et al., 2016; Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Palhano-Fontes et al., 2019; Ross et al., 2016).

In this paper, we systematically review literature from 1940 to 2000 regarding the use of psychedelic drugs in the treatment of ICD-10 anxiety disorders so any supporting evidence can inform future research into the use of psychedelics for treating anxiety disorders.

ICD-10 describes phobic and "other anxiety disorders" under "neurotic, stress related, and somatoform disorders." The grouping "other anxiety disorders" encompasses panic, generalized anxiety disorder (GAD), and mixed anxiety and depressive disorder (World Health Organization [WHO], 1992). In the United Kingdom, anxiety disorders grouped with posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) are the most frequently diagnosed psychiatric conditions with 10% of the population having a "disabling anxiety disorder" at some stage in their life (Fineberg et al., 2013). Despite significant prevalence, many go undetected (Hirschfeld, 2001) and those identified receive far less attention than other areas of mental health (Kessler et al., 2005; Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007).

Patients with anxiety disorders often experience substantial physical and emotional discomfort, functional impairment, reduced work productivity (Erickson et al., 2009; Waghorn, Chant, White, & Whiteford, 2005), elevated rates of substance use and medical illnesses (Roy-Byrne et al., 2008). The natural course of anxiety states is unfavorable, with most patients remaining symptomatic 5–10 years following diagnosis with complete recovery only occurring in 12–25% of cases (Angst & Vollrath, 1991). In the case of GAD, the condition typically persists for a decade or longer and people with a history of GAD will experience lifelong symptoms (Kessler, Keller, & Wittchen, 2001). The Harvard/Brown Anxiety Research Program (HARP) showed that only 15% of respondents attending psychiatric clinics and receiving diverse interventions, and meeting diagnostic criteria for DSM III-R GAD experienced remission for a period exceeding 2 months during the first year. Only 25% had full remission within the first 2 years after baseline (Yonkers, Warshaw, Massion, & Keller, 1994), and 38% within 5 years (Yonkers, Dyck, Warshaw, & Keller, 2000).

The chronic and disabling course of anxiety disorders is also associated with substantial economic and social cost (Bandelow & Michaelis, 2015). In 2010 it was estimated that anxiety disorders cost the European Union €66 m (Andlin-Sobocki & Wittchen, 2005; Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012). A relatively small proportion of the overall cost was attributed to provision of health care, with the major proportion arising from economic costs associated with premature mortality, unemployment, and reduced productivity (Issakidis & Andrews, 2004).

Selective serotonin reuptake inhibitors are now widely considered first-line pharmacological treatment for anxiety disorders. Despite this, withdrawal symptoms and undesirable adverse effects, including insomnia, nausea, nervousness and sexual dysfunction are common with long-term use (Gartlehner et al., 2011).

2 | METHODS

We aim to understand the value of historic publications describing the use of psychedelic drugs in the treatment of anxiety disorders and assess whether this body of evidence supports contemporary research and development in this area. Our search spans the preprohibition period from January 01, 1940 up to January 01, 2000.

The majority of these studies were completed before DSM-III, thus containing dated psychiatric diagnostic classification and terminology. With mental health diagnosis and classification undergoing evolution over time, it was necessary to consider how to fit older diagnostic labels to the present day classification of anxiety disorders. The DSM-I (1952) was the diagnostic classification system used in the United States where most trials of psychedelics were conducted between the 1950s and 1960s. DSM-I states that "the chief characteristic of the psychoneurotic disorders was 'anxiety' which might be directly felt and expressed or which might be unconsciously and automatically controlled by the utilization of various psychological defense mechanisms (depression, conversion, displacement, etc.)" (American Psychiatric Association [APA] Committee on Nomenclature & Statistics, 1958). DSM-I describes six types of psychoneurotic reaction anxiety reaction, dissociative reaction, conversion reaction, phobic reaction, obsessive-compulsive reaction, and depressive reaction (APA Committee on Nomenclature & Statistics, 1958).

The DSM-I diagnosis "psychoneurotic disorder anxiety reaction" is described as follows:

In this kind of reaction the anxiety is diffuse and not restricted to definite situations or objects, as in the case of phobic reactions. It is not controlled by any specific psychological defense mechanism as in other psychoneurotic reaction. This reaction is characterized by anxious expectation and frequently associated with somatic symptomatology. The condition is to be differentiated from normal apprehensiveness or fear. The term is synonymous...
with the former term “anxiety state” (APA Committee on Nomenclature & Statistics, 1958).

DSM has undergone several revisions since 1958 and in the contemporary DSM-5 the closest description to DSM-I “psychoneurotic disorder anxiety reaction” is “generalized anxiety disorder.” We focused on the widely used ICD-10 diagnostic system, which defines “generalized anxiety disorder” as:

The essential feature is anxiety, which is generalized and persistent but not restricted to, or even strongly predominating in, any particular environmental circumstances (i.e. it is “free floating”). As in other anxiety disorders the dominant symptoms are highly variable, but complaints of continuous feelings of nervousness, trembling, muscular tension, sweating, light-headedness, palpitations, dizziness, and epigastric discomfort are common. Fears that the sufferer or a relative will shortly become ill or have an accident are often expressed, together with a variety of other worries and forebodings. This disorder is more common in women, and often related to chronic environmental stress. Its course is variable but tends to be fluctuating and chronic. (WHO, 1992)

Although not discussed explicitly in DSM-I, panic symptoms were described in DSM-II, under the term “anxiety neurosis” where the term “neuroses,” had many similarities to the previous term “psychoneurosis.” Indeed “anxiety neurosis” described a range of symptoms, from anxious over-concern to panic, and was frequently associated with somatic symptoms (Crocq, 2015). In this paper we presume that ICD-10 “panic disorder” is captured by DSM-I “psychoneurotic disorder anxiety reaction.” ICD-10 phobic anxiety disorders are most closely described by the DSM-I diagnosis of “psychoneurotic disorder phobic reaction.”

When outcomes relating to psychoneurotic diagnosis were reported in the studies reviewed, several of the six subtypes were often discussed. The primary aim of this study was to report on ICD-10 anxiety disorders and outcomes for all nondepressive psychoneurosis are reported in tabulated form for completeness.

First, published articles were searched for using Ovid MEDLINE (R) and PsycINFO for the terms: (LSD OR lysergic acid diethylamide OR psychedelic OR hallucinogen OR mescaline OR psicotic OR DMT OR Dimethyltryptamine OR ayahuasca OR psilocybin) AND (therapy OR psychotherapy OR treatment). Following the removal of duplicates, the search returned 1667 articles. Four authors reviewed these search results, selecting papers which described any case reports, series or trials involving human subjects suffering from an ICD-10 anxiety disorder or related disorder. Historic diagnoses were included in this search (see Appendix A).

Subsequently, the Multidisciplinary Association for Psychedelic Studies bibliography (https://maps.org) was searched by the same four authors for the following terms: LSD, lysergic diethylamide, psychedelic, hallucinogen, mescaline, psicotic, DMT, dimethyltryptamine, ayahuasca, psilocybin. This search returned 5,402 entries; these results were manually searched in a similar fashion to the above 1,667, that is among four authors and for the same terms. Subsequent examination of reference lists identified other eligible articles.

The above searches produced a list of 95 articles relating to psychedelic use in the treatment of anxiety-related disorders in humans. These articles were read in full by two teams of two authors, each paper being reviewed by two individuals. Principles of quality assessment in qualitative studies (Pope, Ziebland, & Mays, 2000) and recommendations of the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) initiative were considered.

Twenty-four studies were eligible for inclusion. Appropriate methods for a textual narrative synthesis (Rodgers et al., 2009) were considered. Attention was given to the following: objectives, background, study design, setting, eligibility, defined outcomes, efforts to address bias, study size, statistical methods, outcome data, loss to follow up, generalizability, limitations, source of funding, and particular of the therapy used. It is worth noting that much of this information was not available in the publications reviewed. Data were also tabulated, which guided the discussion (see Figure 1 for an overview of the methodology).

3 | RESULTS

A total of 24 studies published between 1940 and 2000 were included. After examination of the literature, three broad groups of study data emerged. The first group includes four studies that assessed anxiety symptoms or traits of neuroticism across a heterogeneous patient population with a spectrum of psychiatric disorders (Group 1). Often these studies were of more robust designs, with a number of randomized controlled trials (RCTs) using standardized outcome measures and included more thorough descriptions of the methodology employed. Across heterogeneous cohorts in Group 1, 3 studies found a significant reduction in anxiety symptom measures following LSD-assisted psychotherapy from a combined cohort of 95 (Hausner & Dolezal, 1966; Savage, McCabe, Kurland, & Hanlon, 1973; Soskin, 1973; see Table 1). Additionally, a dose dependent reaction was seen in these studies with the exception of Soskin (1973). Conversely, studying abreaction with LSD compared with other agents, Robinson, Davies, Sack, and Morrissey (1963) did not find statistically significant differences in outcome. They do however report that anxiety prone versus passive dependent personalities achieved freedom from symptoms significantly more often (clinician judgment; Robinson et al., 1963). This group of data is useful when considering the high comorbidity of GAD in contemporary epidemiology (Nutt, Argyropoulos, Hood, & Potokar, 2006).

The studies in the first grouping demonstrate consistent psychological screening and preparation for the therapy. Savage et al. (1973) described 20 hr preparation and 38 hr plus of therapy post dosing. Hausner and Dolezal (1966) describes a 2-week inpatient stay before dosing and 6 weeks inpatient stay following treatment. Soskin (1973) describes 6 hr of preparation and 19 standard
psychotherapy sessions in total and Robinson et al. (1963) three times weekly psychotherapy for an unstated period.

In evaluating the anxiety measures deployed in these Group 1 studies, previous investigation has found that most well-established self-report measures of neuroticism or anxiety will have correlations of >0.5. Uluç (2008) found that the Minnesota Multiphasic Personality Inventory (MMPI) is correlated with Beck Anxiety Inventory (BAI) score, α = .72, and Jylhä and Isometsä (2006) found that the Eysenck Personality Inventory (EPI) Neuroticism score has an \( r_s = 0.69 \) (\( p < .01 \)) correlation with BAI score. The Spielberg Trait anxiety scores and EPI Neuroticism have a correlation of \( r = .776 \) (\( p < .01 \); Perkins, Cooper, Abdelall, Smillie, & Corr, 2010), and a correlation of \( r = .79 \) (\( p < .05 \)) was found between EPI Neuroticism scores and Taylor Manifest Anxiety Scale (Meites, Lovallo, & Pishkin, 1980). Although we have not identified a study that assesses correlations between either the Wittenborn Psychiatric Rating Scale (WPRS) Acute Anxiety measure or the Neuroticism N5 and a modern contemporary anxiety measure, it is presumed that a similar correlation exists.

The second group includes extended case series, sometimes including over 100 cases that delineate results for anxiety or phobic psychoneurotic diagnoses that usefully correspond with ICD-10 anxiety disorders (Group 2, see Table 2). These studies are generally open-label and relied on clinical judgment to describe improvements made, a process that often involved triangulation with patients and relatives, with investigators reporting consensus agreements. A total of 14 studies are described, one of which is an individual case study (Brandrup & Vanggaard, 1977) and not included in the summary analysis. For a complete description of the literature reviewed see Appendix B. Combined summary of results from Groups 2 and 3 can be found in (Table 4). Here, results from Chandler and Hartman (1960) have been reported separately, as they reported mean scores for each diagnostic category. Furthermore, results excluding Ling and Buckman (1960) are shown, since an ambiguity in the way they reported the number of successful treatments was noted.

Across Groups 2 and 3, excluding Chandler and Hartman (1960) due to reporting differences, a total of 94 of 145 (64.8%) diagnosed with anxiety reaction and 10 of 25 (40%) diagnosed with phobic reaction were categorized as achieving anything from moderate improvement to full recovery. We note that these results are mirrored in Chandler and Hartman (1960), with anxiety and depressive reaction achieving better mean improvements than obsessive or phobic reactions (Chandler & Hartman, 1960). Across all three groups the sample size ranged from 3 to 379, with a total aggregated sample size of 805 across all the studies. The number of psychedelic sessions ranged from 1 to 58. The most frequently used psychedelic was LSD.
| Study           | Year | Dose LSD (μg) | Sample size (n) | Number of drug therapy sessions | WPRS anxiety | Neuroticism N5 | MMPI anxiety | EPI neuroticism | Pretreatment sessions | Additional therapy                                           |
|-----------------|------|---------------|-----------------|---------------------------------|--------------|----------------|--------------|----------------|-----------------------|-------------------------------------------------------------|
| Robinson et al. | 1963 | 0             | 33              | 0                               |              |                |              |                | 2 assessment meetings. all patients were inpatients         | 3 times weekly, duration unclear                           |
| Anxiety prone personalities improved more than passive 80% vs. 41% (p = .10, p = .20) | Hexobarbitone and methylamphetamine 50-225 | 33              | 8                             |                |              |                |              |                | 3 times weekly, duration unclear                           | 3 times weekly, duration unclear                           |
| Hausner et al.  | 1966 | 0             | 11              | 0                               |              |                |              |                | No change                                          | At least 2 weeks inpatient stay pre-dosing                |
|                 |      |               |                 |                                 |              |                |              |                | 50                    | Various lengths of psychotherapy, all patients stayed for 6 weeks post dosing |
|                 |      |               |                 |                                 |              |                |              |                | 8                     | Various lengths of psychotherapy, all patients stayed for 6 weeks post dosing |
|                 |      |               |                 |                                 |              |                |              |                | 1                    | Various lengths of psychotherapy, all patients stayed for 6 weeks post dosing |
|                 |      |               |                 |                                 |              |                |              |                | Reduction in anxiety (p < .05)                              | 49 hr total, individual and group, 1-week inpatient integration post dosing |
|                 |      |               |                 |                                 |              |                |              |                | 50                    | 38 hr total, individual and group, 1-week inpatient integration post dosing |
|                 |      |               |                 |                                 |              |                |              |                | 350                   | 46 hr total, individual and group, 1-week inpatient integration post dosing |
| Soskin et al.   | 1973 | Librium and ritalin | 14              | 5                               | Reduction in anxiety (p < .01) |                |              |                | 1-2                   | 20                                                                         |
|                 |      |               |                 |                                 | Reduction in anxiety (p < .01) |                |              |                | 50-250                | 20                                                                         |
|                 |      |               |                 |                                 | Reduction in anxiety (p < .01) |                |              |                | 14                    | 20                                                                         |

Note: Studies that assess anxiety symptoms or traits of neuroticism across a heterogenous patient population with a spectrum of psychiatric disorders (Group 1). The standardized measures used include; WPRS anxiety, Neuroticism questionnaire N-5 by Knobloch and Hausner, MMPI anxiety, EPI Neuroticism. Abbreviations: LSD, lysergic acid diethylamide; WPRS, Wittenborn Psychiatric Rating Scale.
with mescaline, psilocybin and a psilocybin derivative (CZ 74) used on occasion. The dose of LSD used ranged from 25 to 1,500 μg. Many studies would titrate doses until an appropriate response to the drug was achieved. In two studies a single large dose of psychedelic without associated psychotherapy was used with the aim of bringing about psychological change following a single "transcendental experience." In both studies a large dose of LSD was administered (range 100–300 μg) with some receiving dose amplification with mescaline (200–400 mg). In many of the studies reviewed, anti-psychotics and barbiturates were used to help terminate the drug effect and often amphetamines were used to augment the experience. Unfortunately, it is not possible to ascertain what effect these concomitant medications might have had on treatment outcomes.

Across all studies there are few phobic patients, despite greater prevalence of specific phobias in modern epidemiological studies (Bandelow & Michaelis, 2015; Kessler et al., 2005). Historically, it was often considered that "free floating anxiety" was more amenable to treatment with psychedelic drugs than phobic anxiety possibly influencing the decision to study psychoneurotic anxiety reaction more often than phobic reaction. The combined results from this review also suggest that generalized anxiety may be more amenable to psychedelic therapy. As discussed previously, GAD is often a chronic condition and recovery is infrequent. Patients categorized by Composite International Diagnostic Interview (CIDI) who have a self-perceived problem and do not receive treatment can expect their BAI scores to decrease by 4.5 points from 17.5 to 13 over the course of a year (van Beljouw et al., 2010).

4 | DISCUSSION

Previous research into the effects of psychedelic drugs has been extensive, however much of the investigation did not follow methodology that would be considered rigorous by today’s standards. Four studies reviewed were of higher quality, randomized control design, but most had numerous methodological issues. Most early studies relied solely on unsubstantiated opinions of therapists. In addition, assessment procedures, follow-up and follow-up evaluation were generally inadequate. No study attempted to control for the effects of intensive patient-therapist involvement. Savage et al. discusses shifting interest from psycholytic to psychedelic therapy, noting that a single dose and the associated briefer therapy is perhaps safer and simpler to investigate (Savage et al., 1973; Savage, Fadiman, Mogar, & Allen, 1966). Similarly, serious methodological shortcomings in psychedelic therapy studies were observed by Mascher (1967). We agree with both observations and echo the conclusion of Rucker, Iliff, and Nutt (2018) "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

Indeed, initial trials were usually little more than case series reported by clinicians who probably had positive expectations about treatment.”

Randomization to placebo and blinding both assessor and participants to the intervention helps modern clinical trials to achieve the rigor that facilitates replication and helps to isolate the effect of the drug from the confounding variables in study setting. However, this becomes problematic when working with psychedelics. There are four reasons why these design strategies are incompatible with psychedelic research (Rucker et al., 2018). The subjective and objective behavioral effects of these compounds are transparent to those familiar, thus blinding is nearly impossible. An indirect consequence of the behavioral transparency was observed by Savage et al. (1973) where "maximum effort" was not always given to the low dose group due to patient and therapist disappointment. Use of placebo is also technically challenging; the absence of such behavioral change is clear, as Sherwood, Stolaroff, and Harman (1962) notes "It would be a trivial procedure to use a placebo because with these dosages no investigator with the slightest understanding of these drugs would fail to detect within 30 min whether placebo or drug had been given." Randomization between doses of psychedelic was suggested by Rucker, Jelen, Flynn, Frowde, and Young (2016) and partially implemented by Savage et al. (1973) as a viable means of mitigating the difficulties in blinding and randomization against controls. The use of control groups had been planned by Whitaker (1964) but they note that "following the remarkable response of the first few patients it was considered unfair to withhold LSD in the interests of experimental design.”

While attitudes towards psychological therapies have shifted since these studies, a key theme cited in the majority of these studies is the importance of pairing psychedelic drug administration with psychological therapy, with therapists almost universally indicating how crucial their input is in the treatment process. Much of the therapy deployed was psychodynamic in nature. Since none of the authors indicate an active decision to adopt this practice, this is likely the result of the predominance of psychoanalysis in the United States at the time (Andreasen, 2007). Sandison, Spencer, and Whitelaw (1954) also state, "we cannot emphasize too strongly, however, that the drug does not fall into the group of ‘physical’ treatments...it should be used only by experienced psychotherapists and their assistants”. Indeed, none of the authors suggest that the positive therapeutic effect can be solely attributed to the pharmacological action of the psychedelic. Chandler and Hartman (1960) warned readers: "The delusion that the drug in itself can produce a cure may be a temptation to the immature therapist.”

Mascher (1967), describes four emerging paradigms in which psychedelic psychotherapy was being used:
| Study (year) | Total sample size (n) | Doses LSD (µg) | Diagnostic (DSM-IV) | Sample size (n) per diagnosis | Number of drug therapy sessions | Worsened (temporary exacerbation) | Unchanged in presentation | Doubtful improvement (either patient or therapist, but not both considered that there had been some improvement) | Slightly improved (some increase in confidence and insight but no real ability) | Some improvement (decrease in severity) | Moderately improved (return to work but some dependence on treatment, possibly worse than pre-treatment) | Improved (mostly recognizable improvement in some areas) | Substantially improved (partial remission of symptoms and increased insight) | Much improved (improved insight, function and work) | Greatly improved (and to treatment, working and functional, occupational return of symptoms) | Recovered / Marked improvement (better than before and symptom free / little change) | Additional therapy |
|-------------|----------------------|----------------|---------------------|-----------------------------|-------------------------------|--------------------------------|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|--------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Weston et al. (2017) | 58 | 25-400 | Anxiety reaction | 22 | 1 to 14 | 5 | 3 | 6 |
| | | | Obsessive reaction | 13 | 5 to 1.5 | 5 | 3 | 4 |
| | | | Depressive reaction | 9 | 10 to 40 | 1 | 3 | 2 |
| | | | Phobic | 3 |  | 1 |  |  |
| | | | Conversion reaction | 5 | 9 to 16 | 2 (refused further treatment) | 1 | 1 |
| Martin (1957) | 58 | 25-100 | Anxiety reaction | 22 | 2 to 14 | 2 | 14 | 5 | 1 |
| | | | Obsessive compulsive reaction | 19 | 2 to 13 | 10 | 6 | 1 |
| Faener & Cohen (1958) | 22 | 25-150 | Anxiety reaction | 3 | 4 to 6 | 1 | 2 | 2 |
| | | | Depressive reaction | 3 |  | 2 |  |  |
| | | | Obsessive compulsive reaction | 1 |  |  |  |  |
| Jang & Raskin (1960) | 39 | 40µg LSD and 5-10mg of Mptdiane | Anxiety reaction | 39 | Unclear | 27 plus achieving moderate to full recovery | | Unclear |
| Chandler & Martinson (1960) | 110 | 20-150 | Anxiety reaction | 27 | 9 | 6.2 (mean) | | Drug sessions formed one facet of long term psychotherapy |
| | | | Depressive reaction | 9 |  | 3 |  |  |
| | | | Obsessive | 3 |  | 3 |  |  |
| | | | Phobic | | 1 |  |  |  |
| | | | Conversion | 1 | Dissociative | 1 | |  |
| Maclean et al. (1941) | 110 | 400-1500 | Anxiety reaction | 100 | 1 | 1 | 7 | 15 | Overnight stay and offer of short to weeks of psychotherapy post drug session |
| | | | Obsessive reaction | 1 | 1 | 1 | |  |
| Sherwood et al. (1962) | 25 | 100-300µg LSD and 200-400mg Mptdiane | Anxiety reaction | 2 | 1 | 1 | 7 | | Not stated |
| Study (year) | Total sample size (n) | Dose LSD (mg) | Diagnoses (DSM-IV) | Sample size (n) per diagnosis | Number of drug therapy sessions | Worse (temporary exacerbations) | Not improved (symptoms as disabling as when sought help/not able to work) | Slightly improved (some increase in confidence and hope, but no real ability) | Doubtful improvement (either patient or therapist, but not both concluded that there had been some improvement) | Some improvement (decrease in severity) | Moderately improved (return to work but some dependence on treatment, but greatly improved (end to treatment, working and social functions, occupational return of symptoms) |Recovered / Marked improvement (better than before and symptom free/ little more) | Additional therapy |
|-------------|---------------------|----------------|-------------------|-----------------------------|-----------------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------|-----------------------------|--------------------------------|--------------------------------|--------------------------------|------------------|
| Whitaker (1964) | 100 100-250 | Anxiety reaction: 6 (1 lost to follow-up) 3.28 (mean) | Depression reaction: 2 (1 lost to follow-up) 3.28 (mean) | obsessive reaction: 7 (1 lost to follow-up) 3.28 (mean) | phobic reaction: 4 (3 lost to follow-up) 3.28 (mean) | conversion reaction: 5 (2 lost to follow-up) 3.28 (mean) | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 |
| Consilin (1964) | 3 400 | Anxiety reaction: 1 | | Obsessive reaction: 1 | | | 1 | 1 | 1 | 1 | 1 | 1 | 3 sessions of psychotherapy | 23 sessions of psychotherapy | 1 |
| Selenski (1966) | 31 25-2000 | Anxiety reaction: 2 | Obsessive reaction: 3 | Phobic reaction: 2 | Conversion reaction: 1 | | 1 | 1 | 1 | 1 | 1 | 1 | Overnight stay | Overnight stay | 1 |
| Martin (1967) | 60 N/A | Anxiety reaction: 1 | Obsessive reaction: 9 | | | | 1 | 1 | 1 | 1 | 1 | 6 | 3 | 3 |
| Baker (1967) | 150 100-2000 | Anxiety reaction: 5 (1 lost to follow-up) | Depression reaction: 11 | Obsessive reaction: 6 | Phobic reaction: 11 | Conversion reaction: 3 | 1 | 1 | 1 | 1 | 1 | 1 | Patients in long term therapy of 3 months to 4 years | Discharged on day of leaving, then 7 follow up sessions | 2 |
| Savage et al (1966) | 243 250-300 mg LSD and 200-400 mg mescaline | Anxiety reaction: 29 | Obsessive reaction: 3 | Phobic reaction: 4 | 1 | 1 | 1 | 1 | 1 | 2 | 1 |

Note: Extended case series that delineate results for anxiety or phobic psychoneurotic diagnoses that usefully correspond with ICD-10 anxiety disorders (Group 2). These studies are generally open label and relied on clinical judgement in assessing the improvements made, a process which often involved triangulating with patients and relatives and reporting consensus agreements. The classifications "worse" to "recovered" are the amalgamated classifications from all studies, we considered that these categories could not be condensed further without misleading the reader. A total of 14 studies are described in group 2 (see Appendix B) of which 1 is a case study of an individual and is therefore not included in Table 2.

Abbreviation: LSD, lysergic acid diethylamide.
| Study/Year | Total Sample Size | LSD (mg/d) | Diagnosis (DSM-I) | Sample Size (n) | Number of Drug Therapy Sessions | Worsened (temporary exacerbation) | Unchanged in Presentation | Doubtful Improvement (either patient or therapist, but not both considered that there had been some improvement) | Slightly Improved (some increase in confidence and insight but no real stability) | Some Improvement (decrease in severity) | Moderately Improved (return to work but some dependence on treatment, possibly worse than pre illness) | Substantially Improved (partially elimination of symptoms and increased insight) | Greatly Improved (and to treatment, working and functional, occasional return of symptoms) | Recovered / Marked Improvement (better than before and symptom free / radical change) | Additional Therapy |
|------------|------------------|------------|------------------|-----------------|-------------------------------|-------------------|--------------------------|--------------------------|--------------------------|---------------------------|------------------------------------------|---------------------------------|------------------------------------------|---------------------------------|-----------------|
| Lewis & Scione (1958) | 23 | 25-500 | Psychoneurosis-anxiety and depressive reaction | 11 | 1 to 25 | 0 or 1 | 3 or 4 | 6 or 7 | Not stated |
| | | | Obsessive compulsive reaction | 11 | 1 to 25 | 1 | 5 | 5 | Not stated |
| Steentjijmen et al. (1964) | 129 | 50-1600 | Anxiety and phobic and compulsive neurotic reaction | 19 | 5 to 58 | 6 | 14 | 13 | Individual and/or group |
| | | | Anxiety and depression | 1 | 15 | 1 | 2 | 1 | NE |
| | | | Anxiety and obsessions | 1 | 19 | | | | NE |
| | | | Chronic neurosis | 2 | 2 | | | | NE |
| | | | Compulsive neurosis | 1 | 1 | | | | NE |
| | | | Obsessive compulsive and bipolar | 2 | 2 | | | | NE |
| | | | Depressive reaction | 3 | 3 | | | | NE |
| Vangsveard (1964) | 24 | Up to 400 | Anxiety, heart neurosis and phobia | 35 | 26.7 average | 3 | 10 | 2 | 33 hours individual, 28 group |
| | | | Depressive reaction | 11 | 26.7 average | 2 | 1 | 6 | 2 | 33 hours individual, 28 group |
| | | | Obsessive reaction | 4 | 26.7 average | 2 | | 2 | 2 | 33 hours individual, 28 group |
| | | | Conversion hysteria | 4 | 26.7 average | | | 1 | 2 | 1 | 33 hours individual, 28 group |

Note: Results from extended case series where the results for anxiety and phobic reactions are pooled with other psychoneurotic diagnosis, (Group 3). Abbreviation: LSD, lysergic acid diethylamide.
| Diagnosis       | Combined N | Number categorised as worse to some improvement | Percentage achieving moderate improvement to recovery | Combined N | Number categorised as worse to moderately improved | Percentage achieving improvement to recovery | Cases (N) reported by Chandler and Hartman (1960) | Mean scores reported by Chandler and Hartman (1960) |
|-----------------|------------|-----------------------------------------------|-----------------------------------------------------|------------|-----------------------------------------------|-----------------------------------------------|--------------------------------------------------|-------------------------------------------------|
| Anxiety reaction| 145        | 51                                             | 94                                                  | 106        | 42                                           | 64                                            | 60.38%                                           | 27                                               |
|                 |            |                                                |                                                     |            |                                               |                                               | 2.5—some to considerable improvement            |
| Depressive reaction | 102     | 40                                             | 62                                                  | 102        | 44                                           | 58                                            | 56.86%                                           | 9                                                |
|                 |            |                                                |                                                     |            |                                               |                                               | 2.6—some to considerable improvement            |
| Obsessive reaction | 100      | 44                                             | 56                                                  | 100        | 47                                           | 53                                            | 53%                                              | 3                                                |
|                 |            |                                                |                                                     |            |                                               |                                               | 1.2—slight to some improvement                 |
| Phobic reaction  | 25         | 15                                             | 10                                                  | 25         | 15                                           | 10                                            | 40.00%                                           | 3                                                |
|                 |            |                                                |                                                     |            |                                               |                                               | 0.7—little to slight improvement               |
| Conversion reaction | 19      | 8                                              | 11                                                  | 19         | 10                                           | 9                                             | 47.37%                                           | 1                                                |
|                 |            |                                                |                                                     |            |                                               |                                               | 2—some improvement                             |
| Dissociative reaction | 1       | 0                                              | 1                                                   | 1          | 0                                            | 1                                             | 100.00%                                          | 1                                                |
|                 |            |                                                |                                                     |            |                                               |                                               | 4—outstanding improvement                      |

Note: Combined results from Group 2 and Group 3 studies by diagnosis. Splitting the data at “some improvement” allowed the inclusion of Ling and Buckman (1960), the more robust test excluding Ling and Buckman (1960) is also shown. Of 94 patients diagnosed with Anxiety reaction, 64.8% achieved moderate improvement to recovery, with 40.00% in the Phobic reaction group achieving moderate improvement to recovery. Results from Chandler and Hartman (1960), which are not included in the combined results, are also presented.
“1 – One single LSD session is provided after an intensive psychosomatic preparation
2 – Repeated LSD sessions are used in combination with individual psychotherapy
3 – The combination of repeated LSD sessions with individual psychotherapy is completed by additional group therapy
4 – Psichotomimetics are applied only in the course of group therapy”

Mascher reports 62.5% success in paradigm 3 with 56%, 56%, and 40% success in paradigm 1, 2, and 4, respectively (Mascher, 1967). The author notes that of the various diagnoses among patients treated with psychedelic psychotherapy “nine papers pointed out particularly good results with anxiety neurosis, up to 70%;” the most favorable result of all psychiatric diagnoses.

The importance of psychotherapy to the treatment process extends beyond the dosing session. Most authors highlighted the importance of good preparation and integration rather than the application of psychodynamic principles. Furthermore, many of the authors comment on the need for openness, caring attitude from staff, lack of hierarchy and the need for personalized interpretation and understanding of material accessed during psychedelic use.

These elements of therapy were discussed far more frequently than the physical setting, though setting was often described. The importance of the psychological state or “set” and the interpersonal and physical “setting” within which the drug is experienced is well established and it has been shown that the therapeutic effect of therapy with psychedelics is greatly affected by these factors (Grinspoon & Bakalar, 1997). The trend amongst modern trials is to offer fewer hours of psychological therapy support.

Although outside the scope of this paper, we felt it important to highlight the patient narrative. It would likely be misguided to apply overly reductive modeling when attempting to understand psychedelics and their psychologically useful mechanism of action. These drugs were seen as therapeutic through their ability to augment psychological therapy. It was observed that of the multiple effects discussed in the literature reviewed, a recurrent theme was the ability of psychedelics to facilitate vivid recovery of early memories (Chandler & Hartman, 1960; Costello, 1964; Eisner & Cohen, 1958; Ling & Buckman, 1960, 1963; Martin, 1957; Sandison & Whitelaw, 1957; Savage, Hughes, & Mogar, 1968). For interest, we have included an account of a psychedelic experience. It should be noted that the language used to describe the patient and their experience may seem dated to the contemporary reader:

Case B: Female, age 34, married, 2 children. This patient’s marriage was near dissolution. Her motivation for taking LSD was to find “freedom to love without fear, freedom from the burden of self… to know what my true self is.” “I do not like myself—because of self-deception, deceiving others, cruelties I have inflicted on those I cared for… I am very moody… I am afraid of almost everything. I am in desperate and constant need of approval and reassurance… I am sick at some of my own motivations… I do not think I am capable of love”.

Her session was revealing, although not all pleasant; the early portion had in part to do with facing some of the many things she feared, and with coming to terms with her own guilt. Some of her most significant insights are best communicated in her own words: “Our misery comes from within, not without... Forgive yourself for what you did in ignorance, blindness, and fear, and let go -- and you will find death not a thing to fear but a new and exciting experience, merely another level of Reality and Existence... I am the universe, I am all men... I was blind before; all the things I did were only a desperate search for meaning to my life and trying to discover myself. I regret past errors, cruelties, lies, faithlessness, and so forth. But I have lived with self-loathing and find it accomplishes nothing. I find I can forgive myself and not spend time weeping over spilt milk. What was done was done. I did them. It is over--I am reborn. I have punished myself enough. It is time to live--and do better in light of what I have learned... These thoughts seem to hit with absolute truth from nowhere--not the result of analysing.”

Several months after the session, the subject reports that the new insights have resulted in marked improvement in all the areas of her life where she sought help. “Some changes have automatically occurred in me: others I must work at all the time... I would give up anything rather than lose what I have learned.” Sherwood et al., 1962

This extract captures the potentially profound impact of the psychedelic experience and we believe conveys the importance of extensive accompanying psychological therapy to prepare for, manage and integrate patient experiences.

Lastly, we note important described adverse events. Savage et al. (1968) describes a transient psychosis and a manic reaction. Chandler and Hartman (1960) report a suicide in a patient with a history of previous suicide attempts, depression, alcohol and drug addiction. Chandler and Hartman (1960) also describe a patient who self-harmed on several occasions and another that suffered a “temporary psychosis” lasting until the end of the treatment day. Despite these reports, we echo Rucker et al. (2018) in stating “Side effects, or adverse events, during the experience were generally not reported systematically, if at all.” Defining possible adverse events and side effects should form a major focus of future work in this area (Rucker et al., 2018). However, modern psychedelic drug trials do not point towards frequent occurrence of concerning adverse events. The first double-blind, placebo-controlled studies to examine the safety and efficacy of LSD and psilocybin in the treatment of anxiety associated with life-threatening diseases observed, in order of decreasing incidence, clinically nonsignificant blood pressure elevations, headaches and migraines, nausea, transient anxiety, transient paranoia and transient thought disorder (Gasser et al., 2014; Grob et al., 2011; Ross et al., 2016).
5 | CONCLUSION

Despite adverse events and methodological shortcomings, it is clear that a pattern emerges from the review of studies reported here. With a large majority of patients treated for generalized anxiety achieving notable improvement in symptoms over the course of treatment, these findings warrant further investigation.

Psychological therapies have some success in the treatment of anxiety disorders but are often lengthy, occurring at a time when the patient is distressed and seeking timely relief, additionally, they are expensive, consequently limiting their availability. On the illness burden of their cohort, Chandler and Hartman (1960) observed that "the very few patients who could be considered acceptable candidates for orthodox analysis made extremely rapid strides with LSD therapy and showed very little emotional disturbances between sessions." In this paper we find evidence suggesting that in the appropriate context and with sufficient preparation, psychedelic-assisted psychotherapy has the potential to facilitate improvement of anxiety symptoms and disorders, and that this potential should be further explored in contemporary research of more rigorous methodology.

6 | LIMITATIONS

The principles of quality assessment in qualitative studies as outlined by Pope et al. (2000) and recommendations of the STROBE initiative were considered. Studies with usable outcome measures included were often diverse, relying on various standardized measures but also commonly clinician judgment. The varying quality of the evidence was not amenable to formal assessment with cochrane risk bias tools, as few studies fit the requisite RCT design.

CONFLICT OF INTERESTS

King’s College London receives grant funding for phase 1 and 2 trials with psilocybin, led by James Rucker and Allan Young, from COMPASS Pathways Ltd. James Rucker has attended trial related meetings paid for by COMPASS Pathways Ltd. N. W., C. B., A. D., and G. K. have received research funding from COMPASS Pathways Ltd. COMPASS Pathways Ltd. had no influence over the inception, design, execution or publication of this study. A. Y. has received honoraria for attending advisory boards and presenting lectures for Allergan, Astra Zeneca, Biomoniccs, Eli Lilly, Janssen, LivaNova, Lundbeck, Servier, Sumitomo Dainippon Pharma, and Sunovion; and has received consulting fees from Johnson & Johnson and LivaNova. Professor Young receives research funding from the National Institute for Health Research (NIHR) Biomedical Research Centre and South London and Maudsley NHS Foundation Trust and King’s College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

DATA AVAILABILITY STATEMENT

The data that support the findings of this systematic review are from previously reported studies and datasets which have been cited. The processed data are available from the corresponding author, N. W., upon reasonable request.

ORCID

Neil M. Weston https://orcid.org/0000-0001-9961-7884
Damian Gibbs https://orcid.org/0000-0003-1145-2611
Catherine I. V. Bird https://orcid.org/0000-0002-8656-6931
Aster Daniel https://orcid.org/0000-0001-8668-2097
Luke A. Jelen https://orcid.org/0000-0001-6398-5239
Allan H. Young https://orcid.org/0000-0003-2291-6952
James J. Rucker https://orcid.org/0000-0003-4647-8088

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APPENDIX A
Adjustment or
Agoraphobia or
Angst or
Anxiety or
Apprehension or
Free-floating or
Excoriation or
Generalized anxiety or
Hoarding or
Hysteria or
Anxiety-depressive or
Neurasthenia or
Neuroses or
Obsessive or
Compulsive or
Panic or
Panophobia or
Pantophobia or
Phobia or
Posttraumatic Stress or
Psychasthenia or
Psychoneurotic or
Selective mutism or
Separation anxiety or
Social Phobia or
Stress reaction or
Trichotillomania or
APPENDIX B
GROUP 1: STUDIES ASSESSING ANXIETY SYMPTOMS IN HETEROGENEOUS PATIENT POPULATIONS

Full results for the studies described in this section are available in Table 1.

Robinson et al. (1963)

With the aim of comparing LSD-25 abreactive therapy against standard therapy, Robinson et al report on a RCT conducted at Roffey Park Hospital, a community focused facility for in-patient treatment of those suffering from psychoneurosis (Robinson et al., 1963). One hundred and one patients, all similar in regard to diagnosis, social status, age, and intelligence were assigned randomly to one of three treatment arms. The first was standard therapy which comprised of individual psychotherapy \( n = (33) \). The second arm used hexobarbitone sodium 0.1 g and methylamphetamine 20 mg plus standard therapy \( n = (33) \). The third arm \( n = (35) \) used standard treatment plus 8 LSD sessions starting at 50 µg and increasing weekly by 25. It is worth noting that each LSD session was terminated after 6 hr with 75 mg of oral chlorpromazine. There were no significant differences between the treatment arms immediately following treatment in terms of either improvement or being symptom free. Personality was assessed by an independent clinician before and after treatment. He was blinded to the opinions reached by members of the treating team and to treatment. These assessment interviews record a significant difference in response to LSD therapy with the anxiety prone individuals improving after LSD more so than those with dependent personalities (80% vs. 41%, \( \chi^2 = 2.432, p = .10, .20 \)). To evaluate the judgement of the clinician it was found that his perspective agreed with the team’s perspective in 78% of cases.

Hausner and Dolezal (1966)

Hausner and Dolezal (1966) conducted a nonrandomized, nonblinded placebo-controlled trial in a therapeutic community, hypothesizing that LSD therapy would accelerate individual and group psychotherapy. They describe four treatment arms; an individual session with LSD 100 µg \( (n = 11) \), a group session with LSD 50 µg \( (n = 8) \) and 16 controls attending the LSD group 5 of whom received a placebo. A doctor and an assistant were present during all sessions with psychotherapy used during the session. Patients were asked to complete a Neuroticism N5 Questionnaire on five separate occasions: before therapy, after 2 weeks spent at RCN, during the LSD and control sessions, following therapy and 1 year after therapy.

\( \chi^2 \) analysis found a significant improvement \( (p < .05) \) in N5 neuroticism score at 1-year post dosing in the 100 µg individual group compared with the 50 µg group therapy group and no difference between the 50 µg group and controls. In the discussion, the author notes that those receiving LSD in the group had been unwell for significantly longer (2–3 years) than the control group (6–12 m) and that participants had widely varying types and lengths of psychotherapy before and after LSD sessions. Furthermore they suggest that the therapeutic effect was the result of LSD as a catalyst to the psychotherapeutic process, rather than purely due to its pharmacological effects.

Soskin (1973)

In a double blind, placebo-controlled study conducted at Topeka Veteran’s Administration Hospital, Kansas, A Soskin (1973) investigate the use of LSD as an aid to psychotherapy. Twenty-eight patients were included with 21 reporting chronic anxiety and tension and seven nonpsychotic inpatients. Participants were randomly assigned to either the LSD group \( (n = 11) \) or placebo (Librium 25 mg and Ritalin 25 mg) \( (n = 10) \). A battery of psychometric tests were run, pre, post and 18 months after treatment with patients seen twice weekly over a 13 week period (26 sessions total). Drug sessions commenced with 50 µg of LSD which was titrated up by 50 µg each session until final dose of 250. Both groups showed a significant improvement in anxiety \( (p < .01) \) as measured by the change in Wittenborn Psychiatric Scales (WPRS) pre- and post-treatment. We note the small sample size of this trial and the author considers that similar levels of improvement between groups could have been due to the fact that they were hospitalized.

Savage et al. (1973)

Savage et al. (1973) report on a study involving 96 patients with the aim of assessing the overall efficacy and dose response for LSD augmented psychotherapy (Psychoanalytic therapy) against conventional treatment of “the chronic, severe neurotic.” Responding to criticism in the past that research involving psychedelics had previously lacked scientific rigour, they adopt a double-blind RCT design, with controls assigned randomly to three groups matched for age and hours of preparation. All patients were symptomatic with a psychoneurotic diagnosis. The three arms of the study consisted of a treatment as usual group (mainly group therapy) single low dose (50 µg oral LSD; \( n = 32 \)) plus psychotherapy group and high dose (350 µg oral LSD; \( n = 31 \)) plus psychotherapy group.

All forms of treatment resulted in a reduction in anxiety symptoms as assessed by the Minnesota Multiphasic Personality inventory MMPI Factor A (Anxiety) and Eysenck Personality Inventory (EPI) N (Neuroticism) scores, with high-dose LSD subjects scoring significantly lower \( (p < .01) \) on MMPI Anxiety and EPI Neuroticism after treatment than those receiving group therapy. Low dose LSD subjects also showed a significant reduction in MMPI Anxiety and EPI Neuroticism versus group therapy subjects \( (p < .05) \). The authors considered the results ungeneralizable due to poor response rates and interestingly, they note that due to the practical difficulties of blinding when using psychedelic drugs, “maximum effort” was not always given to the low dose group due to patient and therapist disappointment.
GROUP 2: STUDIES DELINEATING ANXIETY, PHOBIC AND OTHER PSYCHONEUROTIC DIAGNOSIS THAT USEFULLY CORRESPOND WITH ICD-10 ANXIETY DISORDERS

Full results for the studies described in this section are available in Table 2

Sandison and Whitelaw (1957)

In an open label case series at Powick Hospital in Worcester, Sandison and Whitelaw (1957) follow up on their paper from 1954 (Sandison et al., 1954). Here they include data from a further 58 patients introduced to psycholytic therapy. The starting dose of LSD was usually 25 mg, with the dose gradually titrated until an adequate reaction was obtained with the maximum dose of 400 µg reported. Of those with a diagnosis of Primary Anxiety neurosis, 17 showed a moderate or significant improvement while five did not improve. Of the three with phobic reaction, one was able to discontinue treatment and resume normal life at an equal or superior level to that attained before the illness began and another improved greatly. The authors comment that over the 3-year period, results convinced them that LSD is powerful adjunct to psychotherapy in neurotic illness, in particular for obsessional and anxiety groups accompanied by mental tension.

Martin (1957)

Martin (1957) report on an open label case series at the Marlborough Day Hospital with the aim of assessing the utility of LSD in chronic psychoneurotic disorders in day-patient conditions. A total of 50 patients with long standing psychoneuroses were included all of whom were required to have a “good” personality, some knowledge of their unconscious processes, some degree of insight, high intelligence and a strong desire to get well. Initially, 25–50 µg of LSD was administered and this was titrated up at each session until the optimal reaction was achieved. A trained nurse and psychiatrist were on standby and the reaction was terminated after 6 hr using 50 mg of Chlorpromazine. Of those with Chronic tension states—1 recovered, 5 were greatly improved, 14 were slightly improved, 2 were not improved. A follow-up 2 years later showed that nine cases had relapsed, mostly from the chronic tension class, when they had been unable to continue with psychotherapy following the LSD treatment.

Eisner and Cohen (1958)

In this study Eisner and Cohen set out to determine whether a short series of LSD treatments combined with psychotherapy could create positive change inpatients with neurotic and/or character diagnoses (Eisner & Cohen, 1958). Twenty-two patients with a range of diagnosis were given LSD on a weekly basis with an initial dose of 25 µg, titrated up by 25 µg to a max dose of 150 µg. There was agreement between patient, clinician and a close contact that two of the three patients with a diagnosis of chronic anxiety showed improvement following treatment.

Ling and Buckman (1960)

In 1960, Ling and Buckman used LSD in psychotherapy with the hope that this might expedite the psychotherapeutic process (Ling & Buckman, 1960). They report on a series of open label cases. The majority of treatments were conducted alone, however a spouse could be present if preferred and between treatments, patients could telephone a therapist. Forty micrograms of LSD was given intramuscularly together with 5–10 mg of methedrine on a weekly basis over 8 weeks. After 4–6 hr 50 mg of thioridazine or chlorpromazine was used to bring the experience to an end. Of the 39 patients diagnosed with tension or anxiety states, no less than 27 improved and possibly many more (the uncertainty in numbers arises from the method of reporting). Of those that were improved, their outcomes vary from returning to work but with some dependence on treatment to being completely symptom free and functioning at a higher level than before illness onset.

Chandler and Hartman (1960)

Using LSD as a facilitating agent in psychotherapy, Chandler and Hartman (1960) report on 110 cases using LSD inpatients that had sought private psychotherapy of their own volition. An average of 6.2, fortnightly LSD sessions were conducted per patient, each lasting 4–4.5 hr. Initial doses were 25–50 µg with a dose of 150 µg reached by the fourth or fifth session. An antagonistic drug was given half an hour before the time to terminate the session; secobarbital 100 mg and/or chlorpromazine hydrochloride 50 mg. Outcome ratings were based on a clinical assessment of presenting symptoms and functional improvement. These were checked for collateral agreement and amalgamated with the patient’s own perspective. Of the 27 patients diagnosed with an anxiety reaction, a mean rating of 2.5 was given, that equates to “some to considerable” improvement while those with phobic reactions achieved a mean score of 0.7 mean score, equating to “little to slight improvement.” The authors note that proper preparation was essential, and that a lack of preparation had the effect of slowing down therapy.

MacLean, MacDonald, Byrne, and Hubbard (1961)

Keen to test the hypothesis that LSD-25 treatment could improve psychiatric disorders, MacLean, MacDonald, Byrne, and Hubbard (1961) describe an open label case series of 100 patients, comprising 61 alcoholics and 39 patients with other psychiatric conditions. The treatment approach consisted in administration of a single high dose of 400–1,500 µg LSD-25. The dose given was determined by an assessment of the patient’s defenses; those closer to self-acceptance
were given lower doses. Patients prepared for the experience by writing an autobiography, which a psychiatrist screened, before taking a history. This was followed by several preparatory sessions with a therapist in the 2 days before the LSD treatment. Treatment took place in a quiet room, comfortably furnished and decorated with universal symbols to which the subject could attach their own meaning. The team consisted of psychiatrist (therapist), psychologist (as cotherapist), psychiatric nurse and music therapist. A counselor trained in psychedelic therapy would remain with the patient until bedtime and unlike other studies, no sedative was used as it was felt this might inhibit integration. Of those 23 with a previous anxiety reaction, 15 were much improved, 7 improved and 1 exhibited no change. The authors conclude that a single high dose of LSD-25 therapy is effective in treating anxiety reaction neurosis.

**Sherwood et al. (1962)**

In 1962, Sherwood et al. (1962) published their report of administering "massive" doses of LSD and mescaline in an open label trial. The sessions were held in tastefully furnished, congenial surroundings. Initial dose was 100–200 µg of LSD and then an additional 200–400 mg of mescaline was administered half an hour later. No blinding was attempted with the author noting that "it would be a trivial procedure to use a placebo because with these dosages no investigator with the slightest understanding of these drugs would fail to detect within 30 min whether placebo or drug had been given." Of those diagnosed with anxiety neurosis both were much improved. Sherwood et al. (1962) note that patients receiving a single high dose "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." However, one in five patients suffered from difficult experiences, including paranoia, hostility, and schizophrenic like reactions. During such episodes rescue medication was avoided but if required, chlorpromazine 100–200 mg was used.

**Ling and Buckman (1963) (individual case report)**

In 1963 Ling and Buckman report on a single case of "severe phobic anxiety" and "Generalized anxiety with an uncontrollable urge to pass water" (Ling & Buckman, 1963). Following 3 weekly sessions using 50–70 µg LSD and 20–30 mg of methylphenidate combined with two additional psychotherapy sessions, the generalized anxiety was completely resolved. This case was not included in the evaluation.

**Whitaker (1964)**

In 1964, Whitaker conducts an open label controlled trial to assess whether the results of psychotherapy were significantly improved by the use of LSD as an adjunct (Whitaker, 1964, 1964b). One hundred patients, 51 male and 49 females, were selected. Initially only patients considered amenable to treatment were included. However, after the success of treatments refractory cases were included. Forty-three had been ill for over 10 years, 23 for over 20 years and 30 had failed to respond to various psychotropic drugs and in many cases ECT. A control group was planned, however following the remarkable response of the first few patients it was considered unfair to withhold LSD in the interests of experimental design. Each participant submitted written discussions of their lives and an account of their experience with LSD the day following their session. This was used in integration sessions. Patients were admitted to a single hospital room overnight, LSD 100–250 µg was given by intramuscular injection or intravenous injection together with 200 mg of nicotinic acid by mouth.

The psychiatrist did provide emotional support and when emotional reactions to phantasies were apparent the psychiatrist drew attention to this to encourage integration. The LSD experience was terminated 5 hr later with 100 mg of Chlorpromazine and 100 mg of amyllobarbitone. However, termination was only achieved in 50% of cases thereby making inpatient management essential.

Psychotherapy was given regularly between LSD sessions and patients were encouraged to critically assess any contributions from the psychotherapist during integration psychotherapy and to see himself as a mature individual. Of those six patients with a diagnosis of Anxiety state, two recovered, two were much improved, one had doubtful improvement, and one failed to follow up. Of those four with phobic reaction four failed to follow up and one was much improved.

**Costello (1964)**

In 1964, Costello reports on a series of three patients with pervasive anxiety with the aim of identifying possible psychotherapeutic mechanisms by which LSD takes effect (Costello, 1964). Patients were given 400 µg of oral LSD, and after 6.5 hr 100 mg of Sparine (promazine) was given intramuscularly to end the experience. The treating clinician then reports on perceived change in presentation and possible psychotherapeutic mechanisms underpinning this. One patient with pervasive anxiety made a full recovery following three sessions psycholytic therapy with LSD and remained symptom free 1 year later. Another patient with depression and anxiety made a full recovery lasting until the end of follow up some 2 years later following one LSD session and an unknown number of psychotherapy sessions. One patient with claustrophobia also made a full recovery.

**Solursch (1966)**

Psychoneurotic patients were treated with LSD at Toronto Western Hospital (Solursch, 1966). Patients were admitted to the hospital for at least 24 hr and given between 25 and 2,000 µg LSD (IV or IM). Methamphetamine 30–50 mg (IV) was offered an hour after LSD. Patients were interviewed the following day and at interval for the
subsequent 3–21 months. Two patients with anxiety reaction made some improvement, one patient with a diagnosis of phobic reaction was unchanged and another was improved.

Martin (1967)

In 1967 Martin describes 60 patients in an open label case series undergoing weekly LSD sessions with an unknown dose. The number of sessions ranged from 6 to 65. Psychotherapy was not given between treatments and support was only given to the patient’s emotional needs when necessary. The one case of psychoneurotic anxiety state made a full recovery, as assessed by clinical judgment. Follow-up was completed after 6 years and there were no relapses in either obsessional or anxiety reactions.

Baker (1967)

In 1967, Edward Baker published the results of an open label case series using 100–2,000 µg of LSD in 150 “functioning” nonpsychotic psychiatric inpatients (Baker, 1967). Patients were admitted to a psychiatric ward, placed in a single room and fastened to the bed by a light belt which is locked (“Posey” belt). LSD was then administered IM while a doctor and nurse sat at either side of the bed engaging with the patient through much of the experience. The LSD session was terminated at 13–15 hr by giving chlorpromazine in divided doses up to 1 mg chlorpromazine for every mg LSD. Patients were followed up for 3 months to 4 years and clinician judged ratings were given. Of those with a diagnosis of psychoneurotic anxiety reaction, one was unimproved, two showed some improvement, and one made definite improvement. Of those with a diagnosis of psychoneurotic phobic reaction, one was unimproved, six showed some improvement, two showed some improvement, and one made much improvement.

Savage et al. (1968)

In 1968, Savage et al. (1968) again reports on an uncontrolled, open label study with a single large dose of LSD without conventional interpretive psychotherapy. Their aim was to bring about psychological change following a “transcendental experience.” Two hundred forty-three patients took part in LSD sessions with a dose of 200–300 µg which in some cases was potentiated by 200–400 mg of mescaline. Initially the patient would begin lying down and listening to music with his eyes covered. This would then be followed by sitting upright, looking at various visual stimuli such as images of relatives and landscapes. Sessions were spent in the company of a male and a female companion, one of whom was a physician. Only emotional support was provided and there was no attempt made at interpretation. Fifty to 250 mg of chlorpromazine was offered to help sleep if desired. A crude clinical rating, reflecting symptoms and attitudes was used worse, no improvement, some improvement, substantial improvement, marked improvement. Of the 19 with a psychoneurotic anxiety reaction one was unchanged, seven express some improvement, nine substantial improvement and two marked improvement. Of those four with a phobic reaction, one was unchanged, two showed some improvement, and one marked improvement.

GROUP 3: STUDIES POOLING ANXIETY, PHOBIC AND OTHER PSYCHONEUROTIC DIAGNOSIS

Full results for the studies described in this section are available in Table 3.

Lewis and Sloane (1958)

Inspired by the work of Sandison et al. (1954) and Sandison and Whitelaw (1957) tested LSD psycholytic therapy in a patient population with poor prognosis. The dose in each session varied from 25 to 500 µg of LSD and was administered once weekly with a maximum of 25 weeks of treatment. Patients were seen by a psychiatrist on the days preceding and following treatment, and for approximately 45 min during the “peak” of the drug reaction. In total, 23 patients were treated 11 of which had a “miscellany of psychoneurotic syndromes, most frequently embracing anxiety and depression.” Of those experiencing anxiety and depression, at least six were improved and the authors note “the drug provided a useful aid to the psychotherapeutic technique.”

Geert-Jørgensen, Hertz, Knudsen, and Kristensen (1964)

Based at the Frederiksberg Hospital in Denmark in 1964 and then later in 1968, Geert-Jørgensen et al. published a series of case reports describing the use of LSD with inpatients and outpatients (Geert-Jørgensen, 1968; Geert-Jørgensen et al., 1964). Between 5 and 58 treatments were given with the dose ranging from 50 to 1,600 µg. One hundred and fifty-seven people commenced treatment with 129 completing the course. Patients were followed up for up to 3 years and at the final follow up in June 1964, of those 19 patients diagnosed with anxiety, phobic and compulsive neurotic reactions, 13 were improved and six remained unchanged or had deteriorated. A number of severe adverse reactions to treatment were noted; with two completed suicides, one attempted suicide and a homicide, patients with a history or psychosis or depression were excluded from future treatment groups.

Johnsen (1964); Madsen et al. (1996)

Gorden Johnsen, the chief physician of Modum Bads Nerve Sanatorium (MBN) in Norway treated a series of patients with LSD, psilocybin and CZ 74 between 1961 and 1979 (Johnsen, 1964). Three hundred and seventy-nine patients were treated between 1961 and 1979. Again careful attention to preparation was made with patients attending several assessments and preparatory sessions. All were required to
have 10–20 hr of preparatory psychotherapy. During dosing, a therapist and nurse were always present. Patients were asked to write down their experiences during or after treatment and some using a tape recorder. Following treatment, the therapist routinely spent an hour with the patient and again the day after.

**Madsen et al. (1996)**

In 1996, Madsen et al. followed up on the cohort studied by Johnsen in 1964, sending the patients a questionnaire. Two hundred and thirty-nine patients returned questionnaires; 24 with obsessive neuroses (10%), 69 with other psychoneuroses (29%). One hundred and forty-eight received up to 200 µg LSD on its own and 83 received it in combination with 10–30 mg of psilocybin or CZ 74 (10–20 mg) and eight received psilocybin or CZ 74 alone or in combination. Responding to whether the psycholytic treatment had been of any help, 15 of the 24 patients with obsessive neurosis answered unequivocally yes, (63%) and 13 of them were still well after receiving an average of 20 treatments. The data from these questionnaires was not tabulated or included in the summary evaluation since it was gathered some 20 years after the original study.

**Vanggaard (1964)**

Thorkil Vanggaard reports on a series of open label LSD treatments at Powick Hospital England where he selected 24 inpatients at random (Vanggaard, 1964). The frequency of dosing varied from weekly to twice weekly, and the length of treatment and dose varied considerably. In one case, 200 LSD treatments were given and a max dose of 1,500 µg is reported, although the average dose across cases was 400–500 µg. Although this case series did not explicitly measure anxiety reaction as an outcome one patient of the two that presented with predominantly anxiety-related symptoms recovered and the other was greatly improved. Additionally, the general acceptance that psychedelic treatments are best used during a course of psychotherapy is reiterated.

**Leuner (1967)**

In 1967, Hanscarl Leuner of the Psychiatric Clinic of the University of Göttingen in Germany studied 82 of the institution’s most severe and chronic psychiatric patients over 8 years (Leuner, 1967). The team used 30–200 µg of LSD and other psychedelic drugs such as and a psilocybin derivative, CZ-74 in psycholytic therapy. Before treatment, each patient assimilated biographical material and undertook five preparatory interviews. Both individual and group therapy took place on a once or twice weekly basis with the average of 26.7 sessions per patient and an effective treatment time of 214 hr. Therapy was seen as important, facilitating the integration of material to everyday life. Of 15 patients with "anxiety and heart-neurosis or phobia," 2 recovered and were able to work, 10 were greatly improved and able to work, 3 moderately improved but unable to work. Often, "Cure" often did not appear until 3–6 months after completion of psycholytic treatment. There were three adverse reaction; two cases developed severe catatonic agitation and one patient physically assaulted his parents-in-law.

**Brandrup and Vanggaard (1977) (individual case study)**

In this single case study, a 30-year-old man with "incapacitating compulsive-neurotic condition" was treated with a weekly dose of 100 µg of LSD for 57 weeks (Brandrup & Vanggaard, 1977). The patient reported fear of contamination and infection from dog feces that had been triggered by stepping in some 4 years previously. He was performing 200–250 hand washings a day and extensive grooming rituals meaning he "never experienced anxiety." From 4.5 months, symptoms and avoidance reduced. It is important to note that Ritalin 20 mg was also given on sessions 7, 8, and 9. As this was a single case study the data was not included in the summary evaluation.

**APPENDIX C**

Review