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SYSTEMATIC REVIEW OR META-ANALYSIS | Full Access

Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies

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Abstract

Objective

To conduct a systematic review of modern-era (post-millennium) clinical studies assessing the therapeutic effects of serotonergic psychedelics drugs for mental health conditions. Although the main focus was on efficacy and safety, study characteristics, duration of antidepressants effects across studies, and the role of the subjective drug experiences were also reviewed and presented.

Method

A systematic literature search (1 Jan 2000 to 1 May 2020) was conducted in PubMed and PsychINFO for studies of patients undergoing treatment with a serotonergic psychedelic.

Results

Data from 16 papers, representing 10 independent psychedelic-assisted therapy trials (psilocybin = 7, ayahuasca = 2, LSD = 1), were extracted, presented in figures and tables, and narratively synthesized and discussed. Across these studies, a total of 188 patients suffering either cancer- or illness-related anxiety and depression disorders (C/I-RADD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD) or substance use disorder (SUD) were included. The reviewed studies established feasibility and evidence of safety, alongside promising early data of efficacy in the treatment of depression, anxiety, OCD, and tobacco and alcohol use disorders. For a majority of patients, the therapeutic effects appeared to be long-lasting (weeks-months) after only 1 to 3 treatment session(s).

All studies were conducted in line with guidelines for the safe conduct of psychedelic therapy, and no severe adverse events were reported.

Conclusion

The resurrection of clinical psychedelic research provides early evidence for treatment efficacy and safety for a range of psychiatric conditions, and constitutes an exciting new treatment avenue in a health area with major unmet needs.

Summations

- Promising early support for therapeutic effects of psychedelic compounds as adjunct to psychotherapy for mood disorders and addictions.
- Apparent long-lasting effects for weeks/months after single interventions.
- The nature of the psychedelic experience is in most studies predictive of mid-term and long-term treatment outcomes.

Limitations

- Despite the promising efficacy and safety results presented in this review, evidence for psychedelic therapy is to be considered preliminary at this stage.
- Additional evidence from ongoing and future larger-scale controlled studies using placebo or comparator conditions and or multiple doses will allow for firmer conclusions about both efficacy and safety.

1 INTRODUCTION

Inspired by early reports on the unique subjective effects of lysergic acid diethylamide (LSD) in the late 1940s-early 1950s, psychedelic compounds became widely used among psychologists and psychiatrists in both research and clinical practice in the 1950–1960s. In total, an estimate of more than 40,000 patients underwent “psychedelic psychotherapy” over a period of about 15–20 years, and by 1961 over 1000 papers had been published on the clinical science of LSD, psilocybin, DMT, and mescaline.[1]

Psychedelics were initially tested in a series of studies comparing their acute effects to the symptoms of schizophrenia, later creating the rationale for a biochemical theory on model psychosis.[2, 3] However, the most significant aspect of the psychedelic research in that period was on these compounds’ therapeutic potential. Studies were carried out for a range of psychiatric indications, hereunder in patients suffering chronic alcoholism,[4-15] obsessive neurosis,[16-19] chronic pain,[20] opioid dependence,[21] and anxiety associated with cancer.[22]

A recent meta-analysis of such early studies of LSD’s therapeutic efficacy for treatment of alcoholism included data from more than 500 participants, and found evidence for a beneficial effect of LSD on alcohol misuse.[23] Another recent systematic review of 19 studies of psychedelic therapy for unipolar mood disorders carried out between 1949 and 1973 reported that 79% showed clinician-judged improvement on depressive symptoms after treatment with a psychedelic.[24] Although some studies were of relatively high scientific quality in this period, most did not live up to today's standards in psychological and pharmacological research. Typically, researchers did not pay the same stringent attention to patient screening/inclusion, control groups/conditions, blinding procedures, standardized and continuous clinical assessments, and assessment of side effects—limiting the potential for firm conclusions on the clinical efficacy and safety of this form of therapy.[24]

However, popular and countercultural movements increasingly embraced psychedelics during this period, and in combination with some examples of controversial psychedelic science being carried out,[25, 26] this eventually led to legislations that put an end to this period of early psychedelic research. In addition, it has also been suggested that the introduction of novel conventions about how to conduct state of the art randomized clinical trials, exemplified by the “1962 Drug Efficacy Amendment” to the Federal Food, Drug, and Cosmetic Act in the USA, might have played a role in the field's downfall.[27] The emphasis on context, or “setting,” when conducting psychedelic therapy made it hard to subjugate this therapy to a model mainly aimed for trialing new pharmaceuticals where the focus was on a “pure” pharmacological action. Studies that neglected a therapeutic setting and support generally failed to produce the same positive outcomes.[27] After the main drug provider stopped manufacture and psychedelics were placed in Schedule 1 of the 1970 s controlled substance act in the United States,[28, 29] psychedelic research was effectively ended.

However, over the last couple of decades, a renewed interest in the classic serotonergic psychedelic compounds has emerged from different scientific fields. Neuroscientists currently apply modern brain imaging techniques such as positron emission tomography (PET),[30-33] single photon emission computer tomography (SPECT),[34, 35] magnetic resonance imaging (MRI),[36-39] electroencephalogram (EEG),[40, 41] and magnetoencephalography (MEG)[36] to the study of these drugs in the laboratory, allowing for new and valuable understandings about their brain mechanisms including neuro-correlates of their unique psychological effects.

Outside the laboratory setting, this research is supplemented by naturalistic studies into the impact of the recreational use of psychedelics. Thus, large-scale epidemiological studies in 100,000+ individuals have reported that past psychedelic use is associated with reduced recent psychological distress and suicidality.[42, 43] Naturalistic prospective studies in users of the psychedelic brew, ayahuasca (that has n,n-DMT as its active psychedelic), in religious contexts support these findings; with first time users showing acute reductions in minor psychiatric distress,[44] as well as reductions in personality measures of harm avoidance and reward dependence at six months of follow-up,[45] and more recent prospective surveys have consolidated evidence for improvements in mental health outcomes with psychedelic use, also identifying important ‘contextual’ predictors of response.[46] Long-term ayahuasca use has further been associated with enhanced neurocognitive functioning and mood and with reduced impulsivity.[47] However, cases of serious adverse events such as manic and psychotic reactions in some ceremonial users of ayahuasca have been documented.[48]

Lastly, experimental studies in healthy psychedelic naïve human volunteers, using single administration(s) of classic psychedelics in a controlled and supported setting, have shown improvements in psychological well-being[49] above active placebo, as well as increases in measures of personality trait, “openness to experience”.[50] Intriguingly, these outcomes appear to last for several months—much longer than the pharmacological presence of the actual compounds—with DMT, psilocybin, and LSD all having half-lives of less than 4 hours.[51-53] More recently, researchers have re-targeted intervention with psychedelics toward clinical populations, mainly for treatment of depression, anxiety, and addiction.[54] Typically, psychedelic-assisted therapy involves only one single (or a couple of) session(s) with administration of a moderate to high dose of a psychedelic compound with the aim to evoke peak[53] or mystical-type[55] experiences, characterized by profound meaningfulness, connectedness,[56] accompanied by a sense of oneness or unity.[49, 57]

1.1 Aims of the study

The aim of this systematic review is to collate the literature and provide an overview of the new (post-millennium) wave of clinical studies on the therapeutic effects of serotonergic hallucinogenic drugs in treatment of psychiatric disorders. Specifically, this article will focus on preliminary evidence for the efficacy and safety of these treatments, the duration of their effects, and the role of the subjective psychedelic experience.

2 METHODS

2.1 Search

The Systematic Reviews and Meta-Analysis guidelines (PRISMA) served as guiding principles for the data collection for this review. A systematic literature search was performed using PubMed and PsychINFO databases and was restricted to studies published in English between January 1st 2000 and May 1st 2020. The start of the search period was informed by previous literature reviews that were not able to identify any clinical research trials published between 1982 and 2000.[58, 59] The search was conducted with the following search string: “schizophrenia OR OCD OR cancer OR anxiety OR depression OR PTSD OR substance use OR addiction AND (Psilocybin OR DMT OR LSD OR Mescaline OR Ayahuasca) AND treatment.” The search words were identical in both databases; however, syntax was modified to meet requirements of the individual databases.

2.2 Eligibility criteria

Both single-blind and double-blind placebo-controlled randomized trials, open-label trials, and proof-of-concept trials in mental health patient populations were included. Additional follow-up papers providing long-term data of the clinical trials were also included. Only articles published in peer-reviewed journals were included in the systematic search. Case reports, observational studies, and cross-sectional studies were not included.

2.3 Participants

Adult patients (18 years +) with a psychiatric disorder diagnosed by their general practitioner and/or by structured clinical interview based on DSM or ICD criteria.

2.4 Interventions

Trials included in the review are limited to those administering one or more doses of a classic serotonergic psychedelic drug in a controlled laboratory setting. The term “classic serotonergic psychedelic drug” covers the four drugs: Psilocybin, LSD, Ayahuasca (n,n-DMT), and Mescaline.

2.5 Outcome measures

Only studies assessing primary outcomes using reliable and validated self-report and/or clinician administered symptom rating scales were included.

2.6 Data extraction

All non-duplicated studies were screened by two authors (KA and DE). From each included trial, the following data were extracted: (1) year of publication and names of authors; (2) psychiatric exclusion criteria; (3) participant characteristics (age, ethnicity, gender, diagnosis, previous exposure to drug, and sample size); (4) type of study design (including randomization, blinding, experimental condition groups); (5) type of pharmacological intervention (including type, comparator, dose, frequency); (6) type of non-drug intervention (including description of psychotherapeutic/psychosocial intervention, frequency, and total hours); (7) type of clinical outcome measure (including level of clinical response, clinical remission, symptom reduction, and length of follow-up); (8) assessment of the participants subjective experience during drug effects (including type of instrument used and potential correlations with clinical outcome data); (9) type of side effect measure/collection method (including number of reported side effects).

3 RESULTS

3.1 Study selection

The systematic search identified 671 references. Fourteen references automatically identified as duplicates (Endnote X9). 657 references were screened based on titles and abstracts, and 641 records were excluded in screening, leaving 16 potential research papers. Full-text reports of the 16 identified research papers were assessed according to eligibility criteria. All 16 are included in this systematic review, ten of these papers represent unique clinical trials with oral administration of serotonergic psychedelics; seven trials on psilocybin,[60-66] two trials on DMT/Ayahuasca,[67, 68] and one trial on LSD.[69] Two recent papers[35, 70] provided additional participants and data to their original trials.[64, 68] Outcome data were only extracted from the most recent trials; however, procedures and trial designs were extracted from one or both (including supplementary files). Three papers are pure follow-up studies on the same original trial samples.[71-73]

3.2 Heterogeneity

Because of strong heterogeneity between the trials (trial designs, frequency of drug administration, drug type, and patient populations), a quantitative meta-analysis of the included trials was deemed inappropriate. Two trials, both investigating psilocybin for cancer related anxiety and depression,[65, 66] are however quite similar, but because of missing descriptive statistics (standard deviation and confidence intervals), a meta-analysis of these two trials were not performed. Instead, the extracted data were synthesized narratively. Data from the ten trials are presented in text and synthesized to table form grouped into three broad diagnostic categories: mood and anxiety disorders (n = 4), cancer-related anxiety and depression disorders (n = 4), and substance use disorders (n = 2), and these are listed in Tables 1, 2, and 3, respectively.

3.3 Study characteristics

The included trials covers five different diagnostic groups: cancer-related anxiety and depression disorders[61, 65, 66] [C-RADD], illness-related anxiety and depression disorders[69] [I-RADD), depressive disorders,[35, 64] obsessive-compulsive disorder[60] [OCD], and substance use disorders[63, 74] [SUD]. Four trials[65-67, 72] used a randomized, placebo (including active placebo) controlled, crossover design, allowing for both comparison of the placebo versus active drug effects, and pre-post analyses of the collapsed groups (including crossover subjects) from baseline to follow-up. Four trials[35, 64, 74, 75] were open label allowing for within-group pre-post treatment analyses only. One trial[60] utilized a pre/post-test design, with a randomized order of drug dose administration; however, it provided no comparison between groups. Another trial[61] was designed as a randomized controlled trial; however, it provided no data of the between-group comparison, and thus, it was treated in this review as an open-label trial. Six trials were conducted in the USA, two trials were conducted in Brazil, one in the UK, and one in Switzerland. A total of 201 patients were studied (89 with C-RADD, 12 with I-RADD, 66 with depression, 25 with SUD, 9 with OCD). A total of 188 patients (95 female) received at least one active dose of a serotonergic psychedelic drug (327 unique dosages, 264 active doses, and 63 very low/active placebo doses). Inactive placebos were administered to 54 participants, with 39 of these also receiving a psychedelic because of crossover trial designs. Table S4 presents trial characteristics, including participant characteristics, trial design, pharmacological and psychosocial interventions, and employed clinical outcome measure. Psychiatric exclusion criteria for each trial are listed in Table S5.

3.4 Non-drug psychotherapy interventions

The psychotherapeutic interventions outside the psychedelic session day varied in both quantity and type. Two trials, one investigating psilocybin for C-RADD and one LSD for I-RADD,[65, 69] both delivered integrative psychotherapy, for example, integrating aspects from humanistic, existential, psychodynamic, body-awareness, mindfulness, and cognitive behavioral therapy. In the psilocybin for smoking cessation trial,[74] cognitive behavioral therapy (CBT) was delivered. In the other substance abuse trial in which psilocybin was tested for alcohol dependence,[63] both CBT and motivational enhancement therapy were employed. Three trials (psilocybin for I-RADD, TR-D, and C-RADD)[61, 64, 66] provided structured sessions, defined as psychosocial interventions in Table S6, prior to and following the psychedelic sessions, with focus on building rapport, preparing for, and debriefing/reflecting on, the psychedelic experience. They did however not explicitly state information regarding type of therapy provided thus providing uncertainty about the content of these sessions. Three trials (psilocybin for OCD, and two trials testing ayahuasca for depression)[35, 60, 67] did not provide any sort of psychotherapy or psychosocial interventions to their participants. A vote counting table was created to present individual trial variables related to procedures and psychosocial/psychotherapeutic interventions (Table S6 in supplementary).

3.5 Depression rating scales

Across the included papers, depression was measured with the following scales: Beck's depression inventory [BDI],[76] Montgomery-Åsberg Depression Rating Scale [MADRS],[77] Hamilton Depression Rating Scale [HAM-D],[78] GRID Hamilton depression rating scale 17 [GRID-HAM-D-17],[79] Snaith-Hamilton Pleasure Scale [SHAPS],[80] Quick inventory of depressive symptomatology self-report [QIDS-SR],[81] Profile of Mood States [POMS],[82] and the depression subscale of the Hospital Anxiety and depression Scale [HADS-D].[83] BDI, QIDS-SR, POMS, SHAPS, and HADS-D are self-rated measures of depression, while MADRS, HAM-D, and GRID-HAM-D-17 are clinician administered.

3.6 Anxiety rating scales

Measures of anxiety was collected using Spielberger's State-trait Anxiety Index [STAI-T & STAI-S],[84] anxiety subscale of the Hospital Anxiety Depression Scale [HADS-A],[83] and Hamilton Anxiety Rating Scale [HAM-A].[85] STAI-T, STAI-S, and HADS-A are patient rated measures, while the HAM-A is a clinician rated instrument.

3.7 Substance use assessments

Measurements of treatment outcome related to substance use/dependence disorders were collected using Time-Line Follow back (TLFB). TLFB is a retrospective calendar for self-report daily substance use.[86] Biological markers of Nicotine dependence were collected in urine and breath. Urine samples were laboratory analyzed for cotinine levels, sensitive to detecting past 6 day use. Breath carbon monoxide (CO) were collected using Bedfont Micro III Smokerlyzer instrument, sensitive at detecting nicotine use past 24 h.[74]

3.8 OCD rating scales

Symptoms of OCD were measured with a patient rated visual analogue scale for overall obsessive-compulsive symptom severity (lacking information regarding which scale) and the clinician administered Yale-Brown obsessive-compulsive scale [YBOCS].[87]

3.9 Subjective experience rating scales

Across the included studies, the subjective drug experience were measured by the following scales: The Mystical Experience Questionnaire 30 item version [MEQ30] and 43 item version (MEQ43),[49, 88] 11-Dimensional altered states of consciousness questionnaire [11D-ASC],[89] 5-Dimensional altered states of consciousness questionnaire [5D-ASC],[90] Hallucinogen rating scale [HRS],[91] and State of consciousness questionnaire [SOCQ].[49] Both the MEQ30 and MEQ43 are embedded within the 100-item States of consciousness questionnaire [SOCQ] and thus requires administration of the SOCQ.[49] See Table **S7** for details.

3.10 Mood and anxiety disorders

In an open-label trial by Sanches and colleagues,[35] 17 patients with recurrent major depressive disorder (DSM-IV diagnosed) participated received one oral dose of ayahuasca (1.76 mg/kg n,n-DMT). In this study, there was no control condition and participants therefore served as their own controls. They had an average HAM-D score of 19.2 at baseline, and their symptoms were assessed at baseline and again at 1, 2, 7, and 21 days post treatment. Participants were admitted to an inpatient ward for a 2-week stay prior to drug ingestion, including a complete taper off any antidepressant medication. None of the participants had any history of illicit drug use or any use of ayahuasca. Significant decreases in scores of depression (HAM-D, MADRS) and scores of anxious depression (subscale of Brief psychiatric rating scale) were observed at all points of assessment post treatment ($p < 0.001$).

Palhano-Fontes and colleagues[67] also tested ayahuasca for treatment of depression. Here, 29 patients with treatment-resistant unipolar depression were randomized to either placebo or one dose of freeze-dried ayahuasca brew (1.1 mg/kg n,n-dmt). All participants had HAM-D score of 18 or more, with a mean of 21.8. All patients had a history of two or more failed antidepressant treatments, and 23 had previously been in psychotherapy. None of the patients had any prior use of ayahuasca. All participants were weaned off their antidepressant medications prior to drug administration, however most were regular users of benzodiazepines. Significant between-group differences with a strong effect size are seen at day seven in favor of the Ayahuasca group ($p = 0.019$, d = 0.98). At day seven, a significant difference in response rate were seen between the ayahuasca group and placebo group, with a clinical response rate of 57% and 20%, respectively ($p = 0.04$). No significant group differences were seen in remission rates, 43% in AYA group vs. 13% in placebo ($p = 0.07$).

In a London-based open-label, uncontrolled study by Carhart-Harris and colleagues, 20 patients with moderate (2/20) or severe (18/20) unipolar major treatment-resistant depression each received two doses of psilocybin.[70] Seventeen patients had previously received some form of psychotherapy intervention, and all participants had a history of unsuccessful treatment of no less than two different antidepressant medication. Psilocybin was administered at a moderate [safety test] dose (10 mg), and one week later followed by a high dose (25 mg). Significant short to mid-term reductions in Quick Inventory of Depressive Symptoms (QIDS-SR16) scores were seen on assessments 1–5 weeks post therapy (d range = 2.1–2.3, $p < 0.001$), as compared with baseline. Long-term assessments revealed sustained effects with significant effects sizes at 3 ($d = 1.5$, $p < 0.001$) and 6 months ($d = 1.6$, $p = 0.004$) follow-up. Significant and sustained effects were also seen on all secondary outcome depression (HAM-D, BDI), anxiety (STAI), and anhedonia (SHAPS) measures at all points of assessment.

Moreno and colleagues[60] recruited 9 TR-OCD patients with obsessive-compulsive disorder (OCD) for a modified double-blind study on psilocybin's treatment efficacy, tolerability, and safety.[60] All participants met DSM-IV criteria for OCD and were required to have at least one earlier treatment failure with an SRI before study enrollment. None of the participants were currently on antidepressant medication during the trial. Participants were given up to four administrations of psilocybin separated by at least one week, in an escalating dosage sequence of 100 μg/kg, 200 μg/kg, and 300 μg/kg. Following the first 100 μg/kg session, each participant received an active placebo-like dose (25 μg psilocybin), which was randomly assigned once at any of the remaining three sessions. Decreases in OCD symptoms score (YBOCS) were observed in all nine subjects at one or more of the testing sessions, and decreases ranged from 23 to 100%. Eight of the nine subjects reported a symptom reduction of ≥25%, while six of them experienced ≥50% symptom reduction, as measured 24 h after at least one of the various psilocybin treatment sessions. One subject qualitatively reported having achieved a sustained long-term remission at 6-month follow-up.

Table 1. Mood and anxiety disorders

Citation	Outcome measure	Assessment and results of primary outcome				Follow-up assessments	
		Day 1	Week 1	Week 2	Week 3	3 Months	6 Months
Palhano-Fontes et al.[67]	HAM-D	*a*	$d = 0.98$*	*a*	*a*	*a*	*a*
Carhart-Harris et al.[70]	QIDS-SR16	*a*	$d = 2.2$***	$d = 2.2$***	$d = 2.1$***	$d = 1.5$***	$d = 1.6$**
	STAI-T	*a*	$d = 2.2$	*a*	*a*	$d = 1.2$***	$d = 1.5$***
Sanches et al.[35]	HAM-D	$d =$ [b],***	$d =$ [b],***	*a*	$d = 2.3$***	*a*	*a*
Moreno		Day 1				6 months	

et al.[60]	YBOCS	Acute and significant symptom reduction seen in all patients at 24-hour assessment following at least one of the dosing sessions post-dose assessments.	One patient in remission as reported on 6-month follow-up (No other data reported)

d = Cohen's *d* effect size statistic.

*=$p < 0.05$, **=$p < 0.01$, ***=$p < 0.001$, bold font=primary outcome measure. Palhano-Fontes show between-group data, all other trials show within-group data.

[a] Data not collected or not reported.

[b] Exact value not reported.

3.11 End-of-life anxiety and depression

Grob and colleagues[61] recruited 12 subjects for a double-blind, placebo-controlled study on psilocybin's anxiolytic effects. Together with a life-threatening cancer diagnosis all participants had a DSM-IV diagnosis of either acute stress disorder, generalized anxiety disorder, anxiety disorder because of cancer, or adjustment disorder with anxiety (number of patients with each diagnosis not reported). Every patient underwent a total of two experimental sessions; one active placebo session (Niacin 250 mg) and one psilocybin session (0.2 mg/kg dose). The order of the drug administration was randomized, with both the treatment staff and patients being blinded to this procedure. Between-group and within-group analysis was conducted. No significant between-group differences were found on any of the outcome measures. Comparing means of the whole group at baseline with scores at follow-up (after both groups received the psilocybin) shows significant reduction in trait anxiety at 1 and 3 months, and in depression at 6-month follow-up.

In a related trial, Peter Gasser and colleagues[69] evaluated the safety and efficacy of LSD-assisted psychotherapy in patients with anxiety related to chronic life-threatening illness (cancer, chronic motor, or autoimmune disease). A total of 12 patients were enrolled for this double-blind, randomized, active placebo-controlled pilot study. All patients had a baseline STAI trait or state score of above 40 and met DSM-IV criteria for an anxiety or depression disorder, with the majority meeting criteria for GAD (n = 6) and/or major depression (n = 7). The participants were allocated to receive two experimental sessions assisted by either active dose LSD (200 µg) or LSD at an active placebo dose (20 µg), separated 2–3 weeks apart. Two months after the final experimental session, the blinding subsided; participants in placebo group were allocated to an additional open-label crossover to the LSD (200 µg) treatment condition. Results at two-month assessment after final experimental sessions show significant between-group differences in state anxiety (p = 0.021, F = 4.846, df = 2,18). Looking at the assessments after all participants have received the full-dose condition (after crossover, post hoc within-group analysis) shows significant reductions of trait and state anxiety at 2 and 12-month follow-up, as compared to scores at baseline.[72]

Griffiths and colleagues[66] more recently conducted a study of psilocybin efficacy in treatment of depressed mood and anxiety in psychologically distressed cancer patients.[66] In addition to a confirmed life-threatening cancer diagnosis, all participants met DSM-IV criteria for the following disorders: chronic adjustment disorder with anxiety (n = 11) or with mixed anxiety and depression (*n* = 11), MDD (*n* = 14), dysthymic disorder (*n* = 6), generalized anxiety (GAD) (*n* = 5), or a combination of GAD and MDD (*n* = 4). Participants were randomly assigned to either a group receiving a placebo-like low-dose first group (1 or 3 mg/70 kg, or to a high-dose first group (22 or 30 mg/70 kg), with a crossover to the opposite condition after 5 weeks. Clinical assessments were performed at baseline, 5 weeks post-dose 1 (prior to second dose), 10 weeks post-dose 1 (5 weeks post-dose 2), and 6 months post-dose 2. Five weeks after the first psilocybin session, the patients who had received the high dose experienced significantly more pronounced decreases in measures of depressed mood and anxiety when compared to patients who had received the low (placebo-like) dose. Thus, clinical significant antidepressant response at 5 weeks post-first drug session was observed for 92% of the patients receiving the high dose, compared with a 32% response rate in patients receiving the low dose. Similarly, significant results were seen for anxiety with clinical response rates of 76% and 24%, for the high- and low-dose group, respectively. Effects were significant, immediately after receiving the high-dose sessions, no matter what order patients received the two sessions. These effects were for both groups sustained at 6 months' follow-up. Thus, at the 6 months of follow-up, there was an average clinical response rate of 83% for anxiety and 78% for depression among the whole group, with remission rates of 57% and 65%, respectively.

In a similar study by Ross and colleagues,[65] 29 cancer patients participated in a randomized, double-blind, placebo-controlled trial assessing the symptom reduction of psilocybin assisted psychotherapy on anxiety and depression associated with life-threatening cancer.[65] All patients met DSM criteria of a psychiatric diagnosis related to anxiety of either adjustment disorder (90%) or GAD (10%). Participants were randomly allocated to two groups, one group receiving psilocybin first and other group receiving a non-active placebo, niacin, first, with a crossover 7 weeks later to the opposite experimental condition. Clinical assessments were conducted 1 day, 2 weeks, 6 weeks, and 7 weeks (1 day prior to second dose) following the first drug dose. Then, 1 day, 6 weeks, and 6 months post-dose 2. The psilocybin first treatment group achieved significant within-group reductions after their psilocybin dose, on all measures on anxiety and depression, as compared with scores at baseline. These reductions were acute (one day after) and significantly maintained at all points of assessment. At 7 weeks after the first psilocybin dose, there were significant clinical antidepressive response rate in 83% of the patients (using BDI) and a 58% anxiolytic response rate by measure of HADS-A (vs. a 14% response rate in the placebo group for both measures). Symptom reductions were also significantly larger than what was seen for the niacin first group for all clinical outcome measure assessments up until the crossover. After receiving their psilocybin dose at crossover, the niacin first group demonstrated within-group symptom reductions similar to the psilocybin first group. For both groups, all clinical outcome scores were significantly reduced at the 8 months' follow-up in comparison with baseline. Response rates at 8 months were ranging from 60 to 80% on all outcome measures (HADS-A, HADS-D, HADS-T and BDI). A recent long-term follow-up on the same sample[73] shows that for the surviving sample (*n* = 15) 60–80% of these participants still met criteria for clinically significant antidepressant or anxiolytic response at 4.5 year follow-up. Additionally, the reductions in hopelessness, demoralization, and death anxiety seen in the original 8 month follow-up were sustained at the 4.5-year follow-up.

Table 2. Depression and anxiety disorders related to cancer and other life-threatening illness

Citation	Outcome measure	Results of clinical outcomes prior to potential crossover				Follow-up assessment's (Within-group results only)	
Griffiths et al.[66]		[a]	[a]	Week 5		6 months	
	GRID-HAM-D	[a]	[a]	*d* = 1.30***		*d* = 2.98***	
	HAM-A	[a]	[a]	*d* = 1.23***		*d* = 3.40***	
Ross et al.[65]		Day 1	Week 2	Week 6		6 months	
	BDI	*d* = 1.10**	*d* = 0.99**	*d* = 1.07**		*d* = 1.03* and 0.93*	
	STAI-T	*d* = 0.95**	*d* = 1.49***	*d* = 1.31***		*d* = 1.72** and 1.13**	
Gasser et al.[69]				2 months post-dose 2		2 months post crossover	12 month post crossover
	STAI-T	[a]	[a]	*d* = 1.1		[b],**	[b],**
	STAI-S	[a]	[a]	*d* = 1.2*		[b],**	[b],**
Grob et al.,[61]				1 month	3 months	6 months	
	BDI	[a]	[a]	t_{11} = –2.17*	[a]	$t^{a}7$ = 2.71*	
	STAI-T	[a]	[a]	t_{11} = 4.36***	t_{10} = 2.55*	[a]	

d = Cohen's *d* effect size statistic.

*=*p* < 0.05, **=*p* < 0.01, ***=*p* < 0.001, bold font = primary outcome measure. Griffiths and Ross show between-group data, except for 6 months follow-up (which represents within-group data only). Gasser and Grob show within-group data only.

[a] Data not collected or not reported.

[b] Exact value not reported, *t* = represents *t*-statistic and is used for studies not reporting *d*.

Table 3. Alcohol and nicotine dependence

Citation	Outcome measures	Results of clinical outcomes				Follow-up assessments
Bogenschutz et al.[63]		Week 5–8	Week 9–12	Week 13–24	Week 25–36	No long-term follow-up
	TLFB AD	*d* = 1.1*	*d* = 0.8*	*d* = 1.1*	*d* = 1.0*	[a]
	TLFB HD	*d* = 1.0*	*d* = 0.7	*d* = 0.8*	*d* = 1.0*	[a]
Johnson et al.[74]; Johnson et al.[71]		10-week duration of the trial				3-year follow-up paper
	TLFB daily cigarette use	11/15 reported quitting on their target quit date				Daily cigarette intake significantly*** reduced at 6, 12 and 30-month follow-

			up for all patients, as compared to baseline
	Breath carbon monoxide (CO) and urine cotinine	These eleven were biologically verified as abstinent during the entire duration of the trial (10 weeks)	Significant* reductions at 6 months, with 12/15 showing seven-day abstinence verified by biomarker assessments. Complete abstinence achieved by 12, 7 and 7 subjects, at 6, 12 and 30 months, respectively

d = Cohen's *d* effect size statistic, *=$p < 0.05$, **=$p < 0.01$, ***=$p < 0.001$, bold font = primary outcome measure.

[a] Data not collected or not reported.

3.12 Substance use disorder

In an open-label trial, Bogenschutz and colleagues[63] assessed the effect of psilocybin treatment in 10 patients with DSM-IV-established diagnosis alcohol dependence. Psilocybin was administered at two separate occasions, first at week 4 (moderate-high dose of 21 mg/70 kg) and second session at week 8 (high dose 28 mg/70 kg). The change in drinking behavior (change in percent heavy drinking days assessed with TLFB) from baseline to 1 to 8 weeks after the first psilocybin session, served as the primary study outcome. Drinking behavior was divided into number of days with any drinking (abbreviated TLFB AD) and number of days in which more than 4 alcohol units were consumed (i.e., heavy drinking, abbreviated TLFB HD). Patients were followed up for 32 weeks after their first psilocybin treatment, and compared with both baseline and the 4-week period prior to psilocybin administration, significant reductions in drinking days and heavy drinking days were observed at all assessment time points throughout this 32-week follow-up period.

In another substance use disorder study, Johnson and colleagues[74] examined the feasibility and safety of using psilocybin treatment to treat smoking dependence. Fifteen nicotine-dependent smokers were included in the trial, and psilocybin was given in up to three sessions. Psilocybin was administered at week 5 (moderate dose, 20 mg/70 kg), week 7 (high dose, 30 mg/70 kg) and week 13 (moderate or high dose, 30 mg/70 kg). Monitoring of smoking cessation consisted of a retrospective self-report calendar assessing smoking days, biomarker analysis of breath carbon monoxide, and urine cotinine. At 6 months' follow-up, 80% of the participants (12/15) were abstinent, and compared with baseline, all participants showed significant reductions in both self-reported daily smoking, urine cotinine, and breath carbon monoxide at this time point.[74] In a recent follow-up paper by the same authors,[71] 67% (10/15) of the participants were still abstinent after 12-months (confirmed by levels of urine cotinine and breath carbon monoxide) with 9 of them abstinent at subsequent long-term follow-up (mean 30 months post-first psilocybin session). Seven of the nine reported continuous abstinence since first psilocybin session.[71]

3.13 Quality of the subjective experience as clinical predictor.

Except for the trial investigating ayahuasca for major depressive disorder,[35] all other reviewed trials collected data on participant's subjective psychedelic experience. Seven of these 9 trials reported on associations between these measures and primary clinical outcomes. Two trials (one investigating psilocybin for I-RADD and one investigating LSD for C-RADD) out of these 9 trials did report collecting subjective experience data but did not provide information about conducting any analyses with such data. For the only trial testing psilocybin for OCD,[60] a non-significant correlation was detected between HRS score and YBOCS score changes.

In the remaining 6 studies (1 x psilocybin for TR-D, 2 x psilocybin for C-RADD, 2 x psilocybin for substance use disorder, and 1 x ayahuasca for depression), the magnitude of the mystical/peak experience during the psychedelic treatment session was found to be a significant predictor of short- and mid-/long-term clinical benefits. Mystical/peak experience predicted short-term clinical outcomes (1–8 weeks) in 5 of these 6 studies,[65-67, 75, 92] and long-term clinical outcome (30 months) in one trial (psilocybin for smoking cessation).[62]

Additionally, non-significant correlations were also found in several trials. As an example, in one trial (investigating psilocybin for cancer-related anxiety and depression) MEQ30 measured on the psilocybin dosing day did not significantly correlate with clinical outcome change scores measured at long-term follow-up after 4.5 years.[73] For a complete overview of the different

mystical/peak experience outcome measures and treatment outcome correlations for each study, please see Table S7.

3.14 Setting

In all trials included in this review, the active drug was administered in quite similar controlled settings. Common for the psychedelic sessions in 9 of 10 of the trials are the following five factors: (1) Session conducted individually in an isolated environment/specific room, (2) treatment personnel present for the patient at all times (either in the same room, or in the room next door), (3) participants instructed to listen to a standardized set of music while lying down on a bed, or in a reclined chair, (4) Limit lightning by dimmed lights, and/or instructing patients to wear eyeshades, (5) treatment staff providing non-directive psychosocial support if needed. The only trial deviating from these five factors was the open-label ayahuasca trial,[35] where the music component was not included. See Table S6 (supplementary file) for tabular overview of each trial setting.

3.15 Adverse events

Apart from the ayahuasca trial by Palhano-Fontes and colleagues,[67] all studies monitored blood pressure (BP) and heart rate (HR). Across studies, BP and HR increases were reported to be transient and dose-dependent (when more than one dose was used,[61, 65]), and typically peaking about 2–3 h post-dose with a subsequent steady return to pre-dose levels toward the end of the sessions. There were no reports of any serious cardiovascular adverse events in any of the trials. With regard to non-cardiovascular side effects, the reporting varied between studies, with some using systematic collections with formal questionnaires and observer ratings,[35, 66, 67, 74] while others relied on less formalized patient reports or structured questioning during follow-up.[60, 61, 65, 69, 70, 75] For the ayahuasca trials, 31 ayahuasca doses were given to 31 patients, and the most common side effects reported purging (n = 16, 52%), nausea (n = 10, 32%), and transient anxiety (n = 7, 23%). Across the psilocybin trials, a total of 145 patients received 268 doses psilocybin. Most common side effects reported among this group were transient anxiety/fear (n = 39, 27%), headache (n = 32, 22%), and nausea or purging (n = 18, 12%). In the single study using LSD, 11 patients received 22 doses of LSD, and the most frequent adverse events were illusions (72.7%), feeling cold (45.4%), and a feeling of abnormality (40.9%). Overall, all reported side effects were mild and transient. See Table S8 for complete overview of reported side effects.

4 DISCUSSION

We systematically reviewed 10 post-millennium psychedelic-assisted therapy studies (16 papers) for mental health indications, with a total of 188 patients being dosed with psilocybin, LSD or ayahuasca/DMT. Overall, these trials established feasibility and evidence of safety, alongside promising early data of efficacy in the treatment of depression / depressive symptoms, anxiety, OCD, and tobacco and alcohol use disorders. Importantly, all the reviewed studies were conducted in line with guidelines for the safe conduct of psychedelic therapy,[93] and no severe adverse events were reported. The most prevalent transient side effects were anxiety/psychological distress, headache and nausea, the latter particularly in ayahuasca studies (Table S8).

The open-label nature and the relatively small scale of most of these reviewed studies warrant some caution when trying to conclude on efficacy of psychedelic-assisted therapies.

This is also the case for a study undertaken by our team, where marked and sustained reductions in depression scores among 20 patients suffering resistant major depression were observed, even at 6 months of follow-up.[70] In support of an antidepressant effect beyond placebo levels, however, comparable efficacies were reported in the two larger controlled studies assessing depressive (and anxiety) symptoms in cancer patients, using non-active placebo[65] or low-dose of psilocybin[66] as control condition. Conclusive evidence for an antidepressant effect may come from the larger-scale multicentre COMPASS Pathways[94] and Usona Institute[95] studies, both of which have received breakthrough status by the US Food and Drug Administration. In these studies, patients with resistant and major depression, respectively, will be randomized to full dose psilocybin condition versus either low/miniscule dose psilocybin as control condition in the COMPASS trial[96] or niacin in the Usona trial.[97] The prediction for these trials is that the antidepressant effect will be dose-dependent and superior to placebo, with the lowest dose of 1 mg being ineffective. Furthermore, our current trial of psilocybin versus the selective serotonin reuptake inhibitor (SSRI), escitalopram,[98] is addressing possible differences in neurobiological mechanisms (e.g., on functional magnetic resonance, fMRI, network connectivity, and amygdala reactivity) behind the antidepressant effects of these two different treatment paradigms. Similarly, more work is required to confirm open-label early evidence of efficacy for treatment of OCD.[60]

The only published modern-era study of psychedelic-assisted therapy for alcohol use disorder supports these observations show significant long-lasting (>8 months) reductions in drinking days following psilocybin administration.[63] In support, a recent meta-analysis of clinical studies in alcohol dependence from the 1950–70s concluded significantly improved odds ratio (OR) for abstinence (OR 2.0) after single high dose of LSD.[23] With the caveat of an open-label design, the observed effect in the study by Bogenschutz and colleagues rivals those of currently available medications for alcohol use disorder: acamprosate vs. placebo OR of 1.9[99]; naltrexone vs. placebo OR of 1.3 [100]; disulfiram vs. other/no treatment OR of 1.6.[101]

In the reviewed study of tobacco dependence,[71, 74] 2–3 psilocybin doses in combination with cognitive behavioral therapy (CBT) for smoking cessation resulted in substantially higher 6 months' smoking abstinence rates than typically observed with other medications or CBT alone.[102] A potential future role in treatment of addiction also finds support from attenuated ethanol self-administration in rodents following administration of psychedelics,[103] as well as from observations in human subjects of reduced consumption and craving of alcohol and other substances following psychedelic use in naturalistic contexts [e.g., in ceremonies].[104-108]

A key shared feature of the range of conditions for which psychedelic therapies show promise —from affective disorders to addictions—is a narrowed, internalized mental state.[109] In depression, patients often find themselves stuck in self-critical rumination about failing and guilt. In addictions, the object of the given addiction—whether it is a substance or a behavior—replaces the negative thinking in depression, resulting in a specific, narrow, and rigid focus, with rumination about seeking the relief afforded by the object. The rationale for using psychedelics in conditions such as OCD, anorexia—and even in binge eating/food addiction in obesity—is consistent given that there is rumination on intrusive thoughts, for example, about contamination or calorie mismanagement.

4.1 Role of the subjective experience

Although the potentially transformative nature of safely supported psychedelic experiences is still poorly understood, interesting discoveries are emerging. Through 5-HT_{2A} receptor agonism, psychedelics dose-dependently[33] produce a wide range of idiosyncratic acute effects on the consciousness of the self and the environment often referred to as “peak” or “mystical” experiences.[53] These are characterized by profound alterations in perception, accompanied by a sense of meaningfulness, insightfulness, and unity,[110, 111] and it has been proposed that the psychedelic state is more malleable, flexible, sensitive to the environment, and open to change.[112, 113] A key feature that makes psychedelic therapy constitute a novel treatment paradigm when compared to conventional pharmacological management of mental health conditions, is the role of these subjective peak experiences. Thus, in most of the reviewed studies, the quality and intensity of the acute psychological experience following psychedelic intake is predictive of the clinical outcomes, that is, reductions in depressive symptoms,[111] alcohol use and craving,[63] and tobacco smoking.[62] For complete overview of such relationships, please see Table S7.

These observations replicate old-era studies in which the psychedelic-induced peak or mystical-type experiences also were observed to predict positive long-term outcomes.[14, 114-117] Similarly, increases in scores of openness to experience[50] as well as psychological well-being[46, 49, 118] following psychedelic interventions have been predicted by measures of the peak experiences in studies of healthy volunteers. Interestingly, the relationship between the peak and subsequent clinical outcome appears to be somewhat specific, in that measures related to peak experiences are significantly more predictive of positive clinical outcomes than, for example, altered visual and auditory perception[111]—thereby giving emphasis to the “psychedelic” (from Greek, meaning “mind-revealing”) rather than the “hallucinogen” effect of these substances. Although not consistently collected in such studies, similar observations have been reported with the non-classic psychedelic or “dissociative” compound, ketamine. Thus, scores related to the mystical-type experience—but not dissociative-type experiences—under ketamine were found to mediate reduced drug use and craving among cocaine dependent individuals.[119]

The increasingly popular phenomenon of using psychedelic compounds in repeated small doses (typically 2–3 doses per week of 5–10% of full tripping doses), so-called “microdosing”, in order to improve mood, well-being, cognition, and creativity,[120] raises the question of whether a full psychedelic experience is required as microdosing is typically understood to be subperceptual. So far, there have been no trials of microdosing for any psychiatric disorder and it seems implausible that a single dose in microdosing range of psilocybin would have as big an effect in depression as the 25 mg psilocybin macrodose usually used. Again, the newly launched depression trials using both micro[as active placebo] and macrodoses of psilocybin will help us understand this better, and additionally, placebo-controlled studies of psychedelic microdosing are on their way.

4.2 Long-lasting therapeutic effects

In addition to the role of the subjective experience, another remarkable difference between psychedelic therapy and the repeated (daily) dosing used in conventional pharmaco-therapy, is the apparent long-lasting therapeutic effects of single psychedelic intervention(s). Of note, psychedelics have plasma half-lives of minutes (DMT[121]) to hours (psilocybin[122] and LSD[123]). Figure 1 gives a visual representation of the reductions over time in depressive symptoms from studies assessing such symptoms, and indicates that treatment effects from psychedelic therapy might last for months. In comparison, the antidepressant effect of the glutamate antagonist anesthetic ketamine, esketamine, ranges from days to weeks[124]—its enantiomer, esketamine, was recently licensed in the USA and Europe for treatment of resistant depression. It is here worth noticing that ketamine, with its history as a drug used in anesthesiology, is typically administered in a medical context without same attention to the setting (such as preparation, psychological integration, room design, light, and music) as in psychedelic interventions. In the future, a direct comparison of ketamine versus psilocybin should be carried out in a randomized design using a *psychedelic setting* and post trip psychotherapy or both drugs, in order to assess duration of effects when given under the same conditions—to see whether the context could affect (further improve/prolong) the treatment effects of ketamine.

Figure 1 Open in figure viewer | PowerPoint

Depression over time (see separate file). A presents depression symptom data for all trials assessing depression, with % score change (from baseline) listed over time. For studies comparing doses between groups, only data from groups receiving a high-dose first are presented. *Y* axis represents depression scores normalized to baseline scores (set to 100%). Psilocybin studies show BDI data, LSD study shows HADS-D data, Ayahuasca study shows HAM-D data.

How to explain these sustained therapeutic effects? Where standard antidepressants protect against the stressors that lead to and perpetuate depression they do not directly affect the underlying cause. In contrast, psychedelic therapy is understood to harnesses a therapeutic window opened up by the brain effects of the drugs to facilitate insight and emotional release and, with psychotherapeutic support, a subsequent healthy revision of outlook and lifestyle.[113] This notion is supported by observations from studies of healthy psychedelic-naive individuals, where the majority of subjects who underwent psilocybin 2–3 administrations rated the psilocybin-occasioned experience as being among the five most personally meaningful and spiritually significant experiences of their lives with subsequent increases in well-being and life satisfaction at follow-up after 14 months.[125] Although the long-lasting effects—maybe even enduring for some individuals—seem very promising, more work needs to be conducted to understand who would benefit from re-dosing when/if the therapeutic [e.g., antidepressant] effects are wearing off. How and when should patients who are relapsing receive a booster intervention session, and could these be conducted more cost effectively than the current use of long [full day] sessions with minimum two professionals present? Could re-dosing happen in a group setting and/or could sessions be shortened, for example, by administering shorter acting psychedelics, such as DMT or 5Meo-DMT, or by using intravenous rather than oral administration of psilocybin [which would shorten the drug effect from 4–5 hrs to around 1 hr]?

4.3 Possible mechanisms

In contrast to conventional antidepressant medication, such as SSRIs, which mainly exert their action pre-synaptically via blockade of mono-amine transporters, psychedelic compound show high affinity and agonist activity at serotonergic receptors; namely 5-HT_{2A} but also 5-HT_{2c}, 5-$HT_{1a/b}$, and LSD also has affinity for dopaminergic receptors and 5-HT_6 and 5-HT_7.[126-129] Notably, blockade of the 5-HT_{2A} receptor in humans, for example, with the 5HT_{2A} receptor antagonist ketanserin, blocks the subjective effects as well as mood-improving effects of psilocybin and LSD,[130-132] and furthermore, the experienced drug intensity under psilocybin is tightly associated with its occupancy on the 5-HT_{2A} receptor as assessed with positron emission tomography (PET).[33]

Evidence suggests that 5-HT_{2A} receptors are centrally involved in affect regulation. Stress can increase 5-HT_{2A} receptor density[133] and affinity[134] in rodents, and elevated 5-HT_{2A} receptor expression has been observed in depressed suicide victims[135] and among unmedicated remitted depressed patients with high traits "pessimism"[136] and "dysfunctional attitudes".[137] Similarly, trait "negativism"[138] and "neuroticism"[139, 140]—the latter a known vulnerability marker for depression[141]—are positively associated with 5-HT_{2A} receptor binding.

Elevated 5-HT_{2A} receptor binding might be related to a low serotonergic state[142] and reflect a compensatory upregulation. Interestingly, LSD reverses deficient avoidance learning,[143] which is consistent with other effective antidepressants,[144] and experimental exposure to LSD and psilocybin causes downregulation of the 5-HT_{2A} receptor in rodents.[145] Similarly, recreational use of psychedelics in humans is associated with reduced cortical 5-HT_{2A} receptor binding as assessed with PET.[146] Also, most antidepressants cause 5-HT_{2A} receptor downregulation,[147] and the antidepressant effect of electro-convulsive therapy (ECT) has been positively associated with downregulation of cortical 5-HT_{2A} receptor.[148] Recently, however, PET scans revealed no detectable changes in 5-HT_{2A} receptor binding 1 week after oral psilocybin administration in a small sample 10 healthy volunteers.[149]

Increased flexible and "divergent" thinking induced by 5-HT2A receptor agonism[150-153] might constitute a central component of the therapeutic action of 5-HT_{2A} receptor stimulation. Importantly, administration of psilocybin[50] and LSD[154] to healthy individuals can lead to increased openness—a trait positively associated with cognitive flexibility.[155] Recreational use of psychedelics is also associated with high openness scores,[156] and recently, sustained increases in openness after psilocybin therapy were detected among patients with treatment-resistant depression—of far greater magnitude than previously observed with conventional antidepressant treatments.[157] Psychedelics likely work by dysregulating activity in systems and circuits that encode inflexible habits of thought and behavior as seen in affective disorders and addictions,[109] allowing them to recalibrate as the acute effects of the drugs subside.[112] Scientists from Johns Hopkins University have suggested that their effects can be conceptualized similar to the model of production of post-traumatic stress disorder (PTSD), but inverted.[62] In contrast to a traumatic event leaving the person with symptoms of avoidance, anxiety, and long-term distress, the psychedelic experience with its flexible brain state offers a profound and meaningful experience could cause lasting, beneficial, and corrective change to the individual's psyche.[50] Studies looking into both the longevity of plasticity-inducing effects as well as the neurobiological mechanisms behind such effects are currently being undertaken in our laboratory at Imperial College using neuroplasticity EEG paradigms—but can also be investigated with PET mapping of synaptogenesis.

In terms of effects on the brain's functional networks, fMRI reveals increases in functional connectivity within the default mode network (DMN) and decreased cerebral blood flow in amygdala one day after psilocybin treatment—the latter negatively correlating with improvement in depression scores.[158] These observations are consistent with studies reporting reductions in DMN functional connectivity [159-161] and with elevated amygdala activity [162-165] among untreated patients with major depression. Interestingly, successful ECT treatment to depressed patients leads to a normalization (increase) of DMN functional connectivity.[161] Other fMRI work has shown that LSD affects cortico-striato-thalamo-cortical (CSTC) feedback loops implicated in the gating of sensory and sensorimotor information to the cortex: LSD diminishes the influence of the striatum on the thalamus and opens the thalamic filter to certain areas of the cortex, including the posterior cingulate cortex.[166]

Another factor to consider when proposing possible mechanisms behind psychedelic therapy is therapeutic alliance between the patient and the therapist. Research on factors common for all psychotherapy traditions suggests that the therapeutic alliance between patient and therapist is one of the most robust and consistent factors that predicts therapy outcome.[167] The construct of therapeutic alliance is centered around two qualities related to therapy practice; the shared affective bond between patient and therapist; and common agreement about the tasks and goals of the therapy.[168] It is possible that the classic psychedelics—as it has been suggested for MDMA in the treatment of PTSD [169]—can increase the affective bond between patient and therapist. LSD increases blood-level oxytocin,[170] which is associated with modulating bonding-like experiences in man.[171] Consistent with this, recent research into the effects of LSD in healthy volunteer's states that LSD has distinct empathogenic effects as it significantly increases the subjects feelings of closeness, openness, trust and happiness.[170] Further research should assess this by incorporating a valid and reliable psychometric measures of therapeutic alliance, one such example being Working Alliance Inventory (WAI) y.[172]

In summary, the resurrection of research into the therapeutic application of psychedelics provides promising pilot data on efficacy and safety in the treatment of a range of mental health conditions. Furthermore, brain imaging work applied to the study of these 5-HT_{2A} agonists are delivering remarkable insights into brain function and instigating an exciting new treatment avenue, namely in the fields of affective disorders and addictions, health areas with major unmet needs.

CONFLICT OF INTEREST

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: D Nutt is advisor at Compass Pathways and AWAKN Life Sciences. R Carhart-Harris is advisor at Entheon Biomedical, Small Pharma, and Synthesis Institute. D Erritzoe is advisor at Field Trip Health And Small Pharma. K Andersen is director at the Norwegian Association for Psychedelic Science (NFPV).

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