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Being no one, being One: The role of ego-dissolution and connectedness in the therapeutic effects of psychedelic experience

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SYSTEMATIC REVIEW,
META-ANALYSIS



ABSTRACT

Background and aims: Despite promising findings indicating the therapeutic potential of psychedelic experience across a variety of domains, the mechanisms and factors affecting its efficacy remain unclear. The present paper explores this by focusing on two psychedelic states which have been suggested as therapeutically significant in past literature: ego-dissolution and connectedness. The aim of the study is to investigate the impact of ego-dissolution and connectedness on the therapeutic effects of the psychedelic experience. **Methods:** The investigation was carried out as a mixed methods systematic review, with the data from four databases analysed thematically and results presented through narrative synthesis. **Results:** The analysis and synthesis of findings from 15 unique studies ($n = 2,182$) indicated that both ego-dissolution and connectedness are associated with a higher chance of improvement following a psychedelic experience. However, there seem to be differences in the way the two experiences affect individuals psychologically. Ego-dissolution appears to trigger psychological change but does not typically exceed the psychedelic experience in its duration, while connectedness can be more sustained and is associated with several positive, potentially therapeutic feelings. **Conclusions:** Moreover, the findings of this review have implications for further theory-building about the mechanisms which enable therapeutic effects in psychedelic experience. This in turn might lead to improved models for psychedelic therapy practice. Emphasis on ego-dissolution during the preparation phase and on connectedness during integration is one suggestion presented here, alongside overarching implications for the mental health debate and general practice.

KEYWORDS

self, oneness, psychedelic therapy, systematic review, mixed methods

INTRODUCTION

Serotonin 2A receptor (5-HT_{2A}R) agonists, also known as classic psychedelics (Vollenweider & Kometer, 2010), have been utilized by humans for millennia. Classic psychedelics can be divided into the sub-classes of tryptamines and phenethylamines with substances like psilocibin, dimethyltryptamine, D-lysergic acid diethylamide (LSD) and ibogaine belonging to the former category and mescaline to the latter (Forstmann & Sagioglou, 2017). Both kinds of psychoactive substances were found to have been used by traditional cultures around the world, as evidenced by the consumption of mescaline-containing San Pedro cacti in the Andes (Sharon, 2000) and *Psilocybe* mushrooms use in Paleolithic Spain (Akers et al., 2011).

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However, it was only upon the first LSD synthesis by Albert Hofmann that widescale scientific investigation into the therapeutic use of psychedelic substances began (Costandi, 2014; Garcia-Romeu & Richards, 2018). The progress in the field was slowed for several decades by legal restrictions due to the “moral panic” around psychedelic substances (Goode, 2008) and their associations with recreational use within anti-war movements (Costandi, 2014). After years of careful revival of the research area, psychedelic therapy is now returning to mainstream science (Aday, Davoli, & Bloesch, 2019).

Psychedelic therapy is usually a tripartite process of preparation, psychedelic session(s), and integration (Johnson et al., 2008). During a psychedelic therapy session, the appropriate dose of a psychedelic for the desired effect is administered. In order to evoke intense and profound psychological experiences researchers usually choose to administer higher doses of the psychedelic substance (Griffiths et al., 2006; Pahnke, 1963), e.g. 25 mg of psilocybin (Carhart-Harris et al., 2017). This takes place in a safe and supervised environment (Garcia-Romeu & Richards, 2018). The evidence for psychedelic therapy’s efficacy has been growing rapidly over the last decade. It has been indicated as an effective tool for reducing depression, anxiety, and anhedonia (Carhart-Harris et al., 2016, 2017) in addition to nicotine (Johnson et al., 2014, 2017), alcohol (Bogenschutz et al., 2015, 2018) and opioid dependence (Brown & Alper, 2018), as well as distress related to terminal illness diagnosis (Griffiths et al., 2016; Grob et al., 2011). It has also been recognized for its potential to improve psychological well-being in general (MacLean et al., 2011), a phenomenon referred to as “the betterment of well people” (phrase coined by Bob Jesse and quoted *inter alia* in Pollan, 2018).

While these initial findings suggest psychedelic experiences could have therapeutic potential for many individuals, understanding of how the therapeutic effects are achieved remains limited. Dose and chemical composition being controlled for, the therapeutic outcome still varies greatly between individuals, depending on the contextual factors before, during and after the psychedelic experience (Carhart-Harris et al., 2018). The factors affecting the individual before and during the session are referred to as the “set and setting” (Leary et al., 1963) and include the psychological state, attitude and expectations of the person ingesting a psychedelic substance (set) as well as the physical and cultural context (setting) in which the experience takes place. Post-session factors include personal assessment of the experience, willingness and ability to change, and support received (Watts & Luoma, 2020). They influence the final stage of psychedelic therapy called integration where a person assimilates new insights and perspectives and processes any challenging experiences which might have arisen during the session.

Even when these factors are optimized according to the current best research, however, the experiential content itself plays a large role in determining the therapeutic outcome by producing insights and perspectives for subsequent integration (Klavetter & Mogar, 1967; Majić et al., 2015).

Among the types of subjective phenomena that a psychedelic might induce, one which has garnered attention since early LSD research (Leary et al., 1964) and is still studied presently (Millière, 2017) is ego-dissolution. It is a state characterized by reduction of self-referential awareness which can occur in various altered states of consciousness, including those caused by ingestion of a psychedelic substance (Nour et al., 2016). Pioneering psychedelic researcher Timothy Leary considered the ability to enter ego-dissolution, without attachment to self, central to a positive psychedelic experience (Leary et al., 1964). A failure to do so can result in “dread of ego-dissolution”, or anxious ego-dissolution, i.e. negatively experienced depersonalization (Studerus et al., 2010). During the more recent wave of psychedelic research, ego-dissolution was found to be occasioned by ingestion of psychedelics such as psilocybin (Griffiths et al., 2011), LSD (Goodman, 2002), or ayahuasca, a brew containing N,N-Dimethyltryptamine (DMT; Trichter et al., 2009).

A phenomenon closely related to ego-dissolution is the sense of boundless unity or connection with one’s surroundings. It has been referred to by different names from oceanic boundlessness (OBN; Dittrich, 1998) to unitive experience (Carhart-Harris et al., 2017) to oneness (Hayes et al., 2020). Use of the term “connectedness” to refer to this phenomenon, as proposed by Watts et al. (2017), seems particularly useful for clinically-oriented psychedelic research as it stands in opposition to disconnectedness, a detrimental state commonly reported by depressed patients before undergoing psychedelic therapy (Watts et al., 2017). Secondly, the related Watts Connectedness Scale (Watts et al., 2022) distinguishes between three distinct kinds of connectedness: with self, with others, and with the world. All three types are believed to be beneficial to an individual’s mental wellbeing and health. This differentiation allows for finer-grained analysis into the potential benefits of each type, which would not be possible using concepts such as OBN or oneness.

The renewed interest in psychedelic research has led to a sufficient number of papers on the effects of psychedelic states being published in the past several years to warrant a review of the field. This has not been done to date for either ego-dissolution or connectedness. Thus, the present systematic review has been carried out to fill this research gap and bring more understanding regarding the specific factors which make the psychedelic experience therapeutic. This could aid creation of improved psychedelic therapy models as well as the introduction of connectedness and ego-dissolution into the wider mental health debate. In terms of the current psychedelic debate, the present piece of research is relevant to the question of the therapeutic importance of psychedelic-induced subjective effects (Olson, 2021; Yaden & Griffiths, 2021). The review will contribute to the discussion by examining the therapeutic consequence of psychedelic phenomenology (through an investigation of two of its elements), which could complement purely biochemical considerations of the mechanisms of action at play in psychedelic therapy.



The primary research aim of the paper is to investigate the extent to which ego-dissolution and connectedness are predictive of the therapeutic effects of psychedelic experience. Additionally, the review analyses whether ego-dissolution and connectedness are associated with each other and if their therapeutic efficacy varies between psychological outcome domains. Only two aspects of “connectedness” as proposed by Watts, i.e., with others and the world/universe, are synonymous with “oceanic boundlessness” and “oneness”. The third category, connectedness with (own) self, does not overlap with these terms sufficiently as for instance oceanic boundlessness can be described as “positively experienced depersonalization” (Studerus et al., 2010) rather than reconnection with the “deeper aspects” of the individual self (Watts et al., 2022). Therefore “connectedness with self” is not investigated in this study. Moreover, the review focuses on psychedelic experiences induced by classic, serotonergic psychedelics (i.e., 5-HT_{2A}-receptor agonists (Pierce & Peroutka, 1989)), due to different mechanisms of action and kinds of experience induced by non-classic psychedelics such as MDMA or ketamine (Carhart-Harris et al., 2014; Glennon et al., 1984).

It was hypothesized that ego-dissolution and connectedness would positively correlate with mental health and wellbeing improvement across different outcome domains. The secondary hypothesis was that ego-dissolution and connectedness would be positively correlated with each other as well.

METHODS

Study protocol

In line with PRISMA recommendations (Moher et al., 2009), this review was pre-registered and its protocol was published with PROSPERO in June 2021 [CRD42021256173].

Eligibility criteria

The review’s inclusion and exclusion criteria were as follows:

1. Population: Participants were eligible for inclusion if they underwent a psychedelic experience induced by a classic psychedelic substance. They would be excluded if they underwent a psychedelic experience induced by either a non-classic psychedelic or means other than administration of a psychedelic substance (e.g., holotropic breathing). The psychedelic substances which were expressly searched for are listed in the search terms (Appendix).
2. Exposure: A portion of participants needed to have experienced ego-dissolution and/or connectedness while under the influence of a psychedelic substance for a study to be included in the review. This would need to have been reported either via a quantitative tool or qualitative recollection. Studies which investigated connectedness as an outcome, particularly “social connectedness” understood as the quality and number of interpersonal

relationships were excluded from the review as this was incongruent with the definition employed here.

3. Comparator: Participants’ wellbeing or mental health at baseline or retrospectively reported as prior to the psychedelic experience was considered a comparator in this review. Alternatively, or additionally, the mental health or wellbeing change was compared between exposed and non-exposed individuals.
4. Outcome: Mental health or psychological wellbeing after a psychedelic experience had to be reported for a study to be included in the review.
5. Study design: Included studies could be quantitative or qualitative in nature. Both interventions and observational studies were considered, as well as dissertations if they were based on original research which would satisfy all the above inclusion criteria. Reviews and meta-analyses were not eligible for the review.

There were no date limits and so the publication dates could range from the beginning of a database collection to July 2021 when the search was re-run prior to final analysis. The review was limited to human samples.

Databases

The databases searched included: MEDLINE, PsycINFO, AMED, and Web of Science. Grey literature was not searched. Journals were not searched manually due to time and resource limitations.

Search terms

The search terms can be found in [Appendix](#).

Study selection

The review management platform Covidence was used for deduplication, title and abstract, and full-text screening. Four reviewers screened titles and abstracts independently and any emergent conflicts were resolved by a third party. The subsequent full-text screening was carried out by one reviewer only, with explicitly stated reasons for all exclusions, as reported in [Fig. 1](#). The same process was repeated when the search was re-run prior to final analysis.

Data collection

The following data was extracted from the included studies (where available):

1. Study characteristics: authorship, year and country, study design, psychedelic substance(s) used, the amount administered, the context in which the psychedelic experience took place, means of investigating ego-dissolution and/or connectedness in participants, mental health and/or wellbeing outcome measures;
2. Participant characteristics: demographics (ethnicity and/or nationality, gender, age), sample size, amount of experience with psychedelic substances, any diagnosed mental health conditions, self-reported mental health or psychological wellbeing problems;



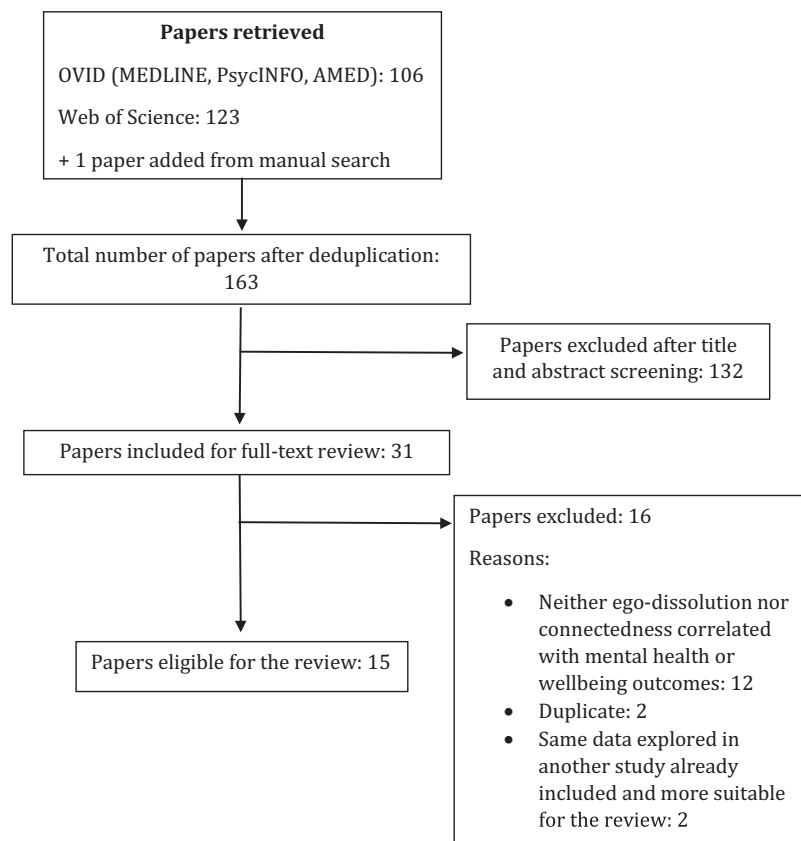


Fig. 1. PRISMA flowchart

3. Results: qualitative and quantitative data (psychometric measures, ratings of the experience, interview transcripts, written accounts).

Risk of bias appraisal

The studies were assessed for trustworthiness, relevance, and usefulness using the Mixed Methods Appraisal Tool (Hong et al., 2018). All studies were assessed against two opening questions: (1) Are there clear research questions? (2) Do the collected data allow to address the research questions? If the study was assessed positively against these initial criteria, it was then evaluated according to further five questions appropriate to its study design (qualitative, quantitative randomized controlled trials, quantitative non-randomized, quantitative descriptive, and mixed methods).

Data synthesis

At the stage of planning of the review, a preliminary search was carried out to assess which methodology should be decided upon. The relevant studies found at the time differed greatly between each other in terms of methodology employed. Focusing on only one study design could limit the number of studies retrieved in the actual database search. It was, therefore, decided that the review would include methodologically heterogeneous studies. For this reason, the data gathered in the review was planned to be synthesized through narrative synthesis.

Extracted quantitative data was transformed into qualitative form, following which all data was analysed thematically (following ESRC's Guidance on Conducting Narrative Synthesis, Popay et al., 2006). The transformation involved ridding the extracted data of scores, ratings and similar numerical data and substituting those with relevant descriptive terms. This could result in phrases such as "positive correlation between oceanic self-boundlessness and mean positive attitude changes" or "lack of correlation between ego-dissolution and DASS ratings at follow-up". During the transformation stage effect sizes were considered to the extent that any significant difference in effect size would also be transformed into qualitative form. This could take a form of contrasting results between outcome domains with phrases like "particularly significant", "very significant" and "significant". Those differences were accordingly reported in the results section. Effect sizes were not compared across studies. Following the textual description of studies, the vote-counting method (Popay et al., 2006) was implemented as the next step of preliminary synthesis.

The analysis was inductive and had as its goal systematic identification of the most important, recurrent themes in data extracted from the reviewed studies (Popay et al., 2006). Relationships between studies were explored using reciprocal translation, a method of synthesizing qualitative data from multiple studies through examination of their similarities to find overarching categories of meaning (Noblit & Hare, 1988). When translation is implemented, the

interpretation of all studies' results builds upon these emergent themes (Popay et al., 2006). The studies' heterogeneity was investigated through an analysis of the relationships between the studies' outcomes and psychedelic substances studied, aspects of methodological diversity (especially the physical context of the psychedelic experience) and study populations (Ryan & Cochrane, 2013).

Lastly, the overall weight of evidence was assessed through critical evaluation of the methodological quality and trustworthiness of the included studies (Popay et al., 2006). This assessment was informed by all the previous steps of data synthesis, particularly the quality assessment. Additionally, the applicability of the results to different populations and cultural contexts was evaluated by comparing the effects of ego-dissolution and connectedness reported in different study populations. Risk of bias within the selected papers was considered at this stage, too. A subgroup analysis of the therapeutic effects of ego-dissolution vs connectedness was carried out as planned prior to the commencement of the review. Moreover, it became apparent at the data extraction stage that a subgroup analysis of mental health outcomes could alike be of value, and thus its results form part of the narrative synthesis as well.

RESULTS

Study selection

The systematic literature search of four databases to July 2021 resulted in a total of 229 title-abstracts which were then deduplicated resulting in 162 unique papers (as presented in Fig. 1). Additionally, one paper on ayahuasca-assisted therapy for addiction (Thomas et al., 2013) was added manually bringing the total of papers to 163. Following title and abstract screening, 132 papers were excluded and 31 were considered in full-text screening. After the full-text examination, 15 papers were included as eligible for the review. Among the excluded papers was Thomas et al. (2013), as one of the studies retrieved through the systematic search – Argento et al. (2019) – was found to be exploring the same data but in a manner more suitable for the review, i.e., with more information on the relationship between participants' psychedelic experiences and their wellbeing post-session, revealed in interviews that this study analysed.

Study characteristics

Extracted characteristics of the 15 eligible studies are presented in Table 1 (study design). The 15 included studies were all published within the last 5 years (2017–2021), with majority of them being carried out in the United States, the United Kingdom, or the Netherlands (six, four and four, respectively), although many studies were conducted across several countries. There were five qualitative studies, eight quantitative, and two with mixed study design.

Participant characteristics

Detailed participant characteristics are presented in Table 2 (study population). Overall, the sample sizes ranged from 9 to 654, bringing the total to 2,182 participants. Their nationality information was available in seven studies ($n = 2,048$), wherein 25% were European (including at least 10% from the United Kingdom), 52% from North America (including at least 36% from the United States), 1% from South America, 1% from Australia, 0.7% from Africa (including at least 0.6% from South Africa), and 0.5% from Asia. The remaining 18% of participants were categorized as coming from "other" countries.

Ethnicity was provided by six papers ($n = 525$), in which 81% were White. The study with the largest sample among them categorized all non-White ethnicities together ($n = 77$). The other five studies ($n = 73$) classified non-White ethnicities separately, among which 10% were Black, 4% were Asian or Pacific Islander, 3% were Hispanic, and 3% were multiracial. Additionally, one study recruited members of an indigenous community from Coast Salish in Canada ($n = 11$).

While all studies provided sex or gender data, within one study (Amada et al., 2020) only 276 out of 418 survey respondents provided researchers with their demographic data. Among the participants from all studies who disclosed their gender, around 28% were female and 70% were male. The remaining 2% identified as "other" or "transgender/gender-fluid". All the samples besides Uthaug et al. (2018) had more males than females.

Risk of bias and results of individual studies

The MMAT user guide discourages presenting the risk of bias numerically as a total score (Hong et al., 2018), therefore a short descriptive evaluation of the studies' quality is presented alongside the summaries of their results in Table 3. One common finding was moderately high attrition rate in surveys and observational studies which might have exaggerated some effects or obscured other relationships. Moreover, some samples were very specific due to inclusion criteria based on clinical diagnoses, or antidepressant use history. The effects of SSRI use on responsiveness to serotonergic psychedelic substances were generally not considered. Lastly, the majority of the studies' findings would be considered not applicable to other cultural contexts due to their homogeneity.

Narrative synthesis

Among the included 15 studies, more of them investigated connectedness (11) than ego-dissolution (10). However, many of them (6) researched both experiences. Despite the significant methodological diversity of the studies, it was possible to group them in several ways during the analysis process.

Study design. Psilocybin was the most frequently researched psychedelic substance across the studies, with seven focusing





Table 1. Study characteristics: design

Author, year	Country	Study type	Design	Substance	Amount	Context	Means of ED/C investigation	Means of MH/ wellbeing investigation
Uthaug et al. (2020)	Czechia	Quantitative	Observational with psychometric tools.	Synthetic 5-MeO-DMT	Various (1–4 inhalations)	[Appendix:] Days-long preparation. Indoors, individual experience with a facilitator.	EDI & 5D-ASC	MH: DASS-21, SWL scale; Mindfulness: FFMQ-39.
Nielson et al. (2018)	US	Mixed	Interview and psychometric tools.	Psilocybin	2 sessions: 0.3 mg kg ⁻¹ first, 0.4 or 0.3 mg kg ⁻¹ second.	Preparation and integration with a psychotherapist.	MEQ & ASC	Reduction in heavy drinking days and interviews.
Amada et al. (2020)	US	Mixed (mostly qualitative)	Survey	All psychedelics	N/A	Various	Open-ended questions on psychedelic experience.	Open-ended questions, scores on the impact and quality of the psychedelic experience.
Watts et al. (2017)	UK	Qualitative	Semi-structured interview with thematic analysis, guided by 3 main questions.	Psilocybin	2 sessions: 10 mg & 25 mg.	Sessions in a relaxed environment with music and 2 guides. Integration sessions post-treatment.	Open-ended questions on psychedelic experience.	Open-ended questions
Roseman et al. (2018)	UK	Quantitative	Experimental within-subject design	Psilocybin	2 sessions: 10 mg & 25 mg.	Pre-session preparation. Music and support of a guide during the sessions. Integration with a psychotherapist.	ASC, PQ	QIDS-SR16, BDI, HAM-D, DAS, STAI, LOT-R, SHAPS. ≥50% from baseline considered a meaningful reduction in depression.
Uthaug et al. (2019)	The Netherlands, Czechia, Spain	Quantitative	Observational with psychometric tools	5-MeO-DMT from the <i>Bufo alvarius</i> toad	Various	Czechia & the Netherlands: outside in nature; Spain: inside (tipi/rented house).	EDI & 5D-ASC	SWL, DASS-21, FFMQ-15, BSI-18

(continued)

Table 1. Continued

Author, year	Country	Study type	Design	Substance	Amount	Context	Means of ED/C investigation	Means of MH/wellbeing investigation
Kettner et al. (2019)	UK	Quantitative	Observational with psychometric tools	Psilocybin, LSD/1P-LSD, ayahuasca, DMT/5-MeO-DMT, <i>Salvia divinorum</i> , mescaline, ibogaine)	Various	Various, assessed for nature involvement.	MEQ, EDI, CEQ.	the WEMWBS, the short form of NR-6
Argento et al. (2019)	Canada	Qualitative	Semi-structured interview with thematic analysis, guided by 3 main questions	Ayahuasca	2 ceremonies, small glasses (50–100 mL). (1 participant took part only once.)	A ceremonial ayahuasca retreat, intended to aid “working with addiction and stress”.	Open-ended questions	Open-ended questions
van Mulukom et al. (2020)	UK & the Netherlands	Quantitative	Survey (descriptive account and several scales)	Classic psychedelics (psilocybin, LSD, DMT, ayahuasca, mescaline, peyote or 5-MeO-DMT)	Various	Various	AWE-S, EDI	IOSS, ECQ, NPI13, Brief Sensation Seeking Scale
Uthaug et al. (2018)	The Netherlands & Colombia	Quantitative	Observational with psychometric tools	Ayahuasca	200 ml of ayahuasca of variable DMT, harmine & harmaline content	Ceremonial	EDI	DASS-21, SWLS, Five Facets of Mindfulness
Belser et al. (2017)	US	Qualitative	Semi-structured interview with IPA	Psilocybin	Within-subject placebo-controlled (2 sessions): psilocybin (0.3 mg kg ⁻¹) or placebo of niacin (250 mg).	Laboratory (clinical trial at NYU)	Open-ended questions	Open-ended questions
Smigielski et al. (2019)	Switzerland	Quantitative	Experimental, double-blind, placebo-controlled	Psilocybin	315 µg kg ⁻¹	5-day mindfulness retreat	5D-ASC & M-scale 6h after	FMI, TMS, MEDEQ. Long-term outcomes: LCI-R at 4-month follow-up. (continued)





Table 1. Continued

Author, year	Country	Study type	Design	Substance	Amount	Context	Means of ED/C investigation	Means of MH/ wellbeing investigation
Noorani et al. (2018)	US	Qualitative	Semi-structured interview with thematic analysis	Psilocybin	1st session: ~0.29 mg kg ⁻¹ 2nd & 3rd sessions: ~0.43 mg kg ⁻¹ .	Smoking cessation pilot study between 2009 and 2015 at Johns Hopkins.	Open-ended questions	Open-ended questions
Agin-Liebes et al. (2021a)	US	Qualitative (enhanced with quantitative data from the original study by Anderson et al. 2020)	Microphenomenological interviews (IPA)	Psilocybin	[Anderson et al. 2020 (parent study):] 0.3–0.36 mg kg ⁻¹	Psilocybin-assisted group therapy for older long-term AIDS survivor men.	Open-ended questions	Open-ended questions (and PCL-5 & ICG-R from previous study)
Agin-Liebes et al. (2021b)	US (based on a larger epidemiological study carried out in the Netherlands)	Quantitative	Survey (retrospective)	Mescaline	Various	Various (naturalistic use)	MEQ, EDI, CEQ	PEQ + open-ended questions on mental health

Abbreviations: 5D-ASC – 5-Dimensional Altered States of Consciousness Rating Scale; 5-MeO-DMT – 5-methoxy-N,N-dimethyltryptamine; AIDS – acquired immunodeficiency syndrome; ASC – Altered States of Consciousness (questionnaire); AWE-S – Awe Experience Scale; BDI – Beck Depression Inventory; BSI-18 – Brief Symptom Inventory-18; CEQ – Challenging Experiences Questionnaire; DAS – Dysfunctional Attitudes Scale; DASS-21 – Depression Anxiety Stress Scale-21; DMT – N,N-dimethyltryptamine; ECQ – Existential Concerns Questionnaire; ED/C – ego-dissolution or connectedness; EDI – Ego Dissolution Inventory; FFMQ-39 – Five Facet Mindfulness Questionnaire; FMI – Freiburg Mindfulness Inventory; HAM-D – Hamilton Depression Scale; ICG-R – Inventory of Complicated Grief; IOSS – Inclusion of Other in the Self Scale; LCI-R – Life Changes Inventory-Revised; LOT-R – Life Orientation Test Revisited; LSD – lysergic acid diethylamide; MEDEQ – Meditation Depth Questionnaire; MEQ – Mystical Experience Questionnaire; MH – mental health; NPI13 – Narcissistic Personality Inventory; NR-6 – Nature-Relatedness Scale; PCL-5 – Posttraumatic Stress Disorder Checklist; PEQ – Persisting Effects Questionnaire; PI – Psychological Insight Questionnaire; PQ – Psychedelic Questionnaire; QIDS-SR16 – Quick Inventory of Depressive Symptomatology; SHAPS – Snaith-Hamilton Pleasure Scale; STAI – Spielberger’s Trait Anxiety; SWL – Satisfaction with Life Scale; TMS – Toronto Mindfulness Scale; WEMWBS – Warwick-Edinburgh Mental Well-being Scale.

Table 2. Study characteristics: population information

Author, date	Demographics (nationality/ethnicity; female to male ratio; age mean (range))	Psychedelic experience	Sample size	Diagnoses	Self-reported psychological issues
Uthaug et al. (2020)	Europe (8), North America (3); 3:8; 33.	All had previous experience (9 no experience with 5-MeO-DMT, 1 used 3×, 1 used 5×)	11	[Appendix:] None. Many conditions screened out based on self-report.	Depression: 4; depression & anxiety: 1, depression & anxiety & PTSD: 1; "other": 1.
Nielson et al. (2018)	N/A, 4:6, 40.1 (25-56).	Exclusion if: used psychedelics >10× or at all in the past 30 days.	10	All met DSM-IV-TR criteria for alcohol dependence.	Excluded if: family history of schizophrenia, bipolar disorder, suicide; cocaine, psychostimulant, or opioid dependence.
Amada et al. (2020)	US (67%), Canada (6%), UK (4%), other parts of Europe (13%), South Africa (3%), Australia (2%), Asia (2%), Central or South America (2%). Only 276 provided demographic information: ~113:163, 38.6 (17-80).	At least 1 past experience required to participate in the survey.	418	N/A	N/A
Watts et al. (2017)	15 White, 3 Black, 1 Asian, and 1 Hispanic; 6:13; (30-64).	5 had experience, 4 in a recreational context in early adulthood.	20	Inclusion for: score of 17+ on the HAM-D and no response to at least 2 different ADs. Exclusion if: personal or family history of psychosis.	N/A
Roseman et al. (2018)	[Carhart-Harris et al. 2017:] 15 White, 3 Black, 1 Asian, 1 Hispanic; 6:14; 44.1 (27-64).	Only psilocybin experience reported: 13 had never taken, 3 once, 1 twice, 3 thrice.	20 (19 completed all the measures)	Inclusion for: major depression of a moderate to severe degree (16+ on the HAM-D), and no response to 2 adequate courses of AD treatment.	N/A
Uthaug et al. (2019)	Europe (34; 81%), Asia (2; 4.8%), Australia (2; 4.8%), South America (3; 7.1%), North America (1; 2.4%); ~17:25; 38.	15 had no experience with 5-MeO-DMT. 92.9% had experience with other psychedelics.	42	Exclusion if: current use of ADs; experiencing schizophrenia or other psychoses; a cardiovascular illness.	No MH condition: 32. Depression: 1; personality disorder: 1; a MH disorder not on the list: 1. Anxiety: 4. "Addiction": 3.
Kettner et al. (2019)	US (199; 30.4%), UK (128; 19.6%), Denmark (60; 9.2%), Germany (32; 4.9%), Canada (32; 4.9%), other - 50 countries in total (203; 31.0%); 165:485 (4 other); 28.9.	Never: 62 (9.5%) Once: 40 (6.1%) 2-5 times: 148 (22.6%) 6-10 times: 106 (16.2%) 11-20 times: 109 (16.7%) 21-50 times: 110 (16.8%) 51-100 times: 39 (6.0%) More than 100 times: 40 (6.1%)	Baseline: 654. Follow-ups: N1 = 379; N2 = 315; N3 = 212; N4 = 64.	N/A	Specific WEMWBS data not provided.

(continued)





Table 2. Continued

Author, date	Demographics (nationality/ethnicity; female to male ratio; age mean (range))	Psychedelic experience	Sample size	Diagnoses	Self-reported psychological issues
Argento et al. (2019)	Indigenous (all from Coast Salish band); 5:6; 38 (19–56).	Inclusion for: no experience with ayahuasca.	11	Exclusion if: current use of SSRIs; current or recent experience of psychosis.	Substance abuse
van Mulukom et al. (2020)	US (251; 60.6%), UK (50; 12.1%), Canada (23; 5.6%), Germany (13; 3.1%), Australia (11; 2.7%), remaining participants from 31 other countries (<10 in each country); 91:310 (13 other); 30 (18–78).	Psilocybin: 179 (45.0%) LSD: 129 (32.4%) DMT: 32 (8.0%) Ayahuasca: 21 (5.3%) Mescaline/peyote: 5 (1.3%) 5-MeO-DMT: 2 (0.5%) Other (including 2C-P and 4-HO-MET): 16 (4.0%) A combination of CSPs: 12 (3.0%) A combination of CSP and non-CSP: 13 (3.3%).	414 had experience with classic serotonergic psychedelics	N/A	Some assessed as maladaptive narcissists through the study procedure.
Uthaug et al. (2018)	Netherlands sample: Europe (93.3%), Asia (3.3%), North America (3.3%); 18:12. Colombia sample: South America (70.4%), Africa (11.1%), North America (18.5%); 18:9. Age not provided.	No past experience with ayahuasca: 13 (43.3%) – Netherlands; 11 (40.7%) – Colombia. Experience with other psychedelic substances: 20 (66.7%) – Netherlands; 19 (70.4%) – Colombia. No experience with other psychedelic substances: 10 (33.3%) – Netherlands; (no information for Colombia).	Netherlands: 30 Colombia: 27	None of the participants were currently on any medication that could have affected their ayahuasca intake.	No MH diagnosis: 23 – Netherlands; 15 – Colombia. Depression: 3 – Netherlands, 4 – Colombia. Anxiety: 1 – Netherlands, 2 – Colombia. Personality disorder: 2 – Netherlands. Addiction: 1 – Netherlands. In Colombia some participants did not answer the related question. N/A
Belser et al. (2017)	12 White, 1 Multiracial; 6:7; 50 (18–76).	No past experience: 7 Some experience: 6	13 selected from the quantitative trial	Inclusion for: life expectancy of at least 1 year and a primary diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety.	N/A
Smigielski et al. (2019)	[SM:] Psilocybin group: 8:12; 52. Placebo group: 8:11; 50. (All expert Buddhist meditation	[SM:] No experience: 11 – psilocybin; 10 – placebo. Less than 3×, over 20 years ago: 6 – psilocybin;	39	Exclusion if: major somatic or neurological disorder; current or past psychiatric disorder or history of a psychiatric	N/A

(continued)

Table 2. Continued

Author, date	Demographics (nationality/ethnicity; female to male ratio; age mean (range))	Psychedelic experience	Sample size	Diagnoses	Self-reported psychological issues
	practitioners with minimum 500 h of lifetime formal meditation practice.) Ethnicity/nationality information not provided.	4 – placebo. More than 3× in the last 20 years: 3 – psilocybin; 5 – placebo. Inclusion for: "no or very limited exposure to hallucinogenic drugs".		disorder in a first-degree relative; alcohol or drug dependence or abuse; current or recent use of substances affecting the nervous system.	
Noorani et al. (2018)	Not provided; 5:7; 54 (31–67).	No experience with CSPs: 5 Some experience with CSPs: 7 Average experience: ~10×, ~30 years before intake to the treatment study.	12	Inclusion for: nicotine dependence (FTCD mean score of 5.1 and range 3–6.)	N/A
Agin-Liebes et al. (2021a)	67% non-Hispanic White, 11% Black, 11% Asian/Native Hawaiian or Other Pacific Islander, 11% Multiracial (White/American & Indian/Alaskan Native); all male; 57.9 (50–64).	N/A	9	Severe PTSD (score above median of the original study's sample); complicated grief in relation to long-term AIDS. Inclusion for: clinically significant level of demoralization (DS-II score of ≥8.)	N/A
Agin-Liebes et al. (2021b)	83% White, 17% non-White; North America (60%), Europe (20%), other (20%); 90:344 (trans/fluid: 18); 38 (SD = 14.4).	Lifetime use of mescaline 1–3: 46% Mescaline used once per year or less frequently: 70%	452	N/A	Depression, anxiety, PTSD, alcohol misuse or drug misuse disorder.

Abbreviations: 2-CP - 2-(2,5-dimethoxy-4-propylphenyl)ethanamine; 4-HO-MET – 4-hydroxy-N-methyl-N-ethyltryptamine; AD – antidepressant; CSP – classic serotonergic psychedelic; DS-II – Demoralization Scale-II; DSM-IV-TR – the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; FTCD - Fagerström Test for Cigarette Dependence; HAM-D – Hamilton Depression Rating Scale; MH – mental health; N/A – not applicable; PTSD – post-traumatic stress disorder; SM – supplementary material; UK – the United Kingdom; US – the United States; WEMWBS – Warwick-Edinburgh Mental Well-Being Scale.



Table 3. Results, including risk of bias appraisal

Author, date	Risk of bias appraisal	Primary MH/wellbeing outcome area	Results*
Uthaug et al., (2020)	<i>Quantitative descriptive.</i> Relevant sampling strategy and representative sample of 5-MeO-DMT users. Appropriate measurements and the risk of nonresponse bias low – 1 out of 11 participants did not return for follow-up. Appropriate statistical analysis.	MH: depression, anxiety. Wellbeing: stress, satisfaction with life and mindfulness.	Positive correlation between post-session ratings of the psychedelic experience (assessed via <u>EDI & 5D-ASC</u>) and post and follow-up session ratings of non-judgement (facet of mindfulness) and satisfaction with life. Negative correlation between ratings of the psychedelic experience (<u>EDI & 5D-ASC</u>) and post and follow-up session ratings depression, anxiety, and stress. <u>Oceanic boundlessness</u> correlated positively with non-judgement and SWL and negatively with depression. <u>Anxious ego dissolution</u> correlated negatively with non-judgement.
Nielson et al., (2018)	<i>Mixed methods.</i> Clear research goal, but no guiding questions for the interviews reported. Quantitative outcome measurement and qualitative data generated through interviews are well integrated and their outputs are adequately interpreted. E.g., participants' accounts of the experience and their MEQ scores were analysed conjunctly. An "outlier" result (Heather) is adequately addressed in the discussion.	MH: reduction in heavy drinking days. Wellbeing: general information gathered through interviews.	One participant (Adam) reported experiencing <u>ego-dissolution</u> during his 2nd session (0.3 mg kg ⁻¹), even though he was glad to have resisted it during the first one. The excerpt suggests a sense of rebirth following the ego-dissolution: "There's the old Adam, then the new Adam without alcohol." He was 1 of 4 participants who had a 100% reduction in heavy drinking days. Another participant (Michelle) reported experiencing a sense of <u>connectedness</u> with "that bigger, ultimate place to be" which led to an epistemic breakthrough and sense of peacefulness (which correlated with her high blissful state score of 92). She also achieved a 100% reduction in heavy drinking days, and her experience alike took place during the 2nd session (0.4 mg kg ⁻¹). Both Michelle and Adam had high intensity scores for the 2nd session. Another participant reporting 100% reduction in heavy drinking days (Heather) had very low MEQ, HRS intensity and ASC blissful state scores.
Amada et al., (2020)	<i>Mixed methods.</i> The quantitative data gathered through two survey questions informs the qualitative accounts on psychedelic experiences which constitute most of the study's data. The integration and interpretation are adequate, however the results of quantitative questions reveal a potential	Wellbeing: assessed based on psychedelic experience's valence and impact rating as well as the descriptive account.	The survey's results include many accounts of ego-dissolution and connectedness experiences. <u>Ego-dissolution</u> was reported to have allowed for a reassessment of life's issues and own self without attachment or judgement and with a clearer, more objective view. Based on the participants' accounts

(continued)



Table 3. Continued

Author, date	Risk of bias appraisal	Primary MH/wellbeing outcome area	Results*
Watts et al., (2017)	<p>sampling bias of the study, i.e. majority of participants reported their psychedelic experiences to have had a major, positive impact on their lives, with only 2% reporting negative changes.</p> <p><i>Qualitative.</i> Clear guiding questions for the interviews stated in the paper. The overarching themes stem clearly from the subthemes which in turn are supported with adequate transcript excerpts.</p>	<p>MH: depression.</p> <p>Both MH and wellbeing assessed through interviews. Participants would have participated in quantitative studies beforehand which included psychometric measurements.</p>	<p>the positive changes to their self-perception were permanent. <u>Connectedness</u> was also commonly reported, in the sense of interconnectedness of self with a larger context, even if those contexts varied between individuals (spiritual, human, natural). Participants reported many lasting effects of the experience, e.g., love for nature, sense of responsibility for others' wellbeing or for the Earth. One of the two main themes that emerged from the series of interviews was "disconnection to connection". The realms in which <u>connectedness</u> was experienced included: senses, self, others, the world/Nature, spiritual principle/God. Some of the lasting effects of the experience were increased connection with friends, family, and strangers as well as more engagement in world affairs. One participant experienced <u>connection</u> to a past abuser where a newfound sense of compassion enabled healing of trauma. Feeling of love was also important in one participant's experience: "[During the dose] I was everybody, unity, one life with 6 billion faces, I was the one asking for love and giving love, I was swimming in the sea, and the sea was me". The effects of the experience were felt by participants for weeks or months afterwards. <u>Oceanic boundlessness</u> (OBN) and <u>dread of ego-dissolution</u> (DED) predicted changes in depressive symptoms up to 5 weeks. <u>OBN</u> was positively correlated and predicted the participants' improvement significantly better than the 2 other elements of ASC it was compared to (i.e., visionary restructuralization and auditory alterations). <u>DED</u> was negatively correlated. Those who experienced "<u>complete</u>" OBN (>0.6) scored better for secondary clinical outcomes (such as trait anxiety, anhedonia, optimism, pessimism) than those who had a "non-complete" OBN. The effect persisted at different time points (1-day, 1-week, 5-weeks, 3-months, and 6-months).</p>
Roseman et al., (2018)	<p><i>Quantitative non-randomized.</i> Measurements are appropriate, outcome data complete and some confounders accounted for (e.g., overlapping treatments at follow-up). The sample's representativeness is limited, due to the very specific inclusion criteria: treatment-resistant depression despite at least two courses of antidepressants, last one stopped at least two weeks ago. The possible antidepressant withdrawal symptoms are a confounder not accounted for.</p>	<p>MH: reduction in depressive symptoms.</p>	<p>(continued)</p>



Table 3. Continued

Author, date	Risk of bias appraisal	Primary MH/wellbeing outcome area	Results*
Uthaug et al., (2019)	<p><i>Quantitative descriptive.</i> Appropriate sampling strategy. Sample representative sample of the European population which constituted 81% of the sample. Measurements and statistical analysis were also adequate. However, there is a moderate risk of nonresponse bias as 33 (40%) out of the 75 recruited participants did not fill in the post-session test battery. And of those who completed post-session measurements, 50% did not return for follow-up. This could bias the sample to participants who had a more positive and/or impactful experience.</p>	<p>MH: depression, anxiety. Wellbeing: stress, satisfaction with life, mindfulness.</p>	<p><u>Ego-dissolution</u> (ED) and <u>connectedness</u> were found not to correlate with each other. <u>ED</u> positively correlated with changes in satisfaction with life and negatively correlated with depression, anxiety and stress (DASS-21, BSI-18) and convergent thinking (PCT) on the day following the 5-MeO-DMT session. However, none of the correlations persisted at the 4-weeks follow-up. <u>Oceanic boundlessness</u> positively correlated with satisfaction with life and negatively correlated with convergent thinking on the day following the 5-MeO-DMT session. <u>OBN</u> had no correlation with any ratings at the 4-weeks follow-up.</p>
Kettner et al., (2019)	<p><i>Quantitative descriptive.</i> Appropriate sampling strategy. Somewhat representative sample: anglophone-centric (50% from US and UK) and with much higher male participation (485 vs 169 women & other). There is a moderate risk of nonresponse bias as only 379 out of baseline 654 participants filled the first follow-up survey. Measurements and statistical analysis were appropriate.</p>	Wellbeing and nature-relatedness.	<p>Only <u>ego-dissolution</u> significantly predicted changes in nature relatedness (NR), with significant interaction between time and EDI scores. NR, in turn, was positively correlated with psychological well-being. Where individuals had low NR scores before the psychedelic experience (below the mean 4.01), the relationship between ego-dissolution and NR was mediated by context, i.e. whether the experience took place in nature or not. Mean NR scores were found to be the highest two years after the experience which suggests a possible positive feedback loop.</p>
Argento et al., (2019)	<p><i>Qualitative.</i> Both the qualitative approach and the data collection method were appropriate to the investigation. The research was further focused with three questions which guided the interviews. Findings are adequately derived and interpreted. There is coherence between all the elements of the study.</p>	<p>MH: addiction. Wellbeing: stress.</p>	<p>An experience of <u>connectedness</u> was common during the ayahuasca ceremony and led to an enhanced sense of connection with spirit and nature following the session, which in turn increased participants' wellbeing. With 1 exception, all participants expressed having pre-existent sense of connection with spirit/nature. Still, in the interview process they indicated that this connection was deepened or reawakened through the ayahuasca ceremony.</p>
van Mulukom, et al. (2020)	<p><i>Quantitative descriptive.</i> Relevant sampling strategy. The sample is representative of Western anglophone countries and has 3× more male than female participants which might be reflective of a bias in the user base of the websites</p>	MH: maladaptive narcissism.	<p><u>Ego-dissolution</u> during a recent psychedelic experience was not associated with increased feelings of connectedness and empathy, unlike the experience of awe. The lasting feelings of connectedness and empathy were in turn</p>

(continued)



Table 3. Continued

Author, date	Risk of bias appraisal	Primary MH/wellbeing outcome area	Results*
	used for recruitment. Measurements were appropriate, the risk of nonresponse bias was low and the statistical analysis appropriate. Referring to connectedness as an element of the psychedelic experience (part of the Awe Experience Scale) as well as the long-term outcome (considered equivalent to “inclusion of self in others”) makes the paper less straightforward than it could be.		associated with reduced levels of maladaptive narcissism. <u>Connectedness</u> – considered an element of awe in this study – predicted lower levels of exploitative-entitled narcissism specifically if it was experienced towards nature or humanity, but not in the case of connectedness with the universe. AWE-S connectedness rating was significantly correlated with the extent to which the experience was considered of spiritual or religious nature.
Uthaug et al., (2018)	<i>Quantitative descriptive.</i> Relevant sampling strategy which yielded a sample representative of ayahuasca retreat goers in both Europe and South America, with majority of female participants on both continents. Measurements and statistical analysis were appropriate, the risk of nonresponse bias low for immediate post-measurement, moderate at 4-weeks follow-up (completed by 54%).	MH: depression, anxiety. Wellbeing: stress, satisfaction with life, mindfulness.	On the day following the ayahuasca ceremony, <u>ego-dissolution</u> negatively correlated with stress and depression and positively correlated with different facets of mindfulness (awareness, non-judgement, and nonreactivity) and with satisfaction with life. Only non-reactivity remained significantly correlated with ego-dissolution scores at the 4-weeks follow-up. Anxiety levels were already low at baseline, and so the observed reduction post-session and at follow-up was insignificant.
Belser et al., (2017)	<i>Qualitative.</i> The right approach and data collection method were chosen for the study’s research goals. Not only are the findings supported by relevant quotes, but the excerpts are also placed in the context of individuals’ life pre-psilocybin to highlight the significance of the reported shifts.	MH: acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety.	7 out of 13 participants expressed the theme labelled “From Separateness to Interconnectedness”. The <u>dissolution of self</u> often resulted in a sense of <u>interconnectedness</u> with people, the planet, or the whole universe. These blissful and comforting experiences left participants with new, lasting feelings of empowerment, self-determination, belonging, and acceptance – in relation to their own communities and the universe. While the insights on interconnectedness of all things were often reported to have been achieved through “direct knowing” and as difficult to put into words, 8 participants felt that they could still access the knowledge in ordinary states of consciousness.
Smigielski et al., (2019)	<i>Quantitative RCT.</i> The participants were comparable at baseline – matched for sex, age, meditation experience, and dispositional mindfulness. Information on	Wellbeing: trait and state mindfulness, changes in behaviour and attitudes.	Optimistic attitude toward life and openness significantly predicted the variance in <u>oceanic boundlessness</u> measure as well as mysticism. Psilocybin intake and <u>ego-</u>

(continued)



Table 3. Continued

Author, date	Risk of bias appraisal	Primary MH/wellbeing outcome area	Results*
Noorani et al., (2018)	<p>ethnicity/nationality not provided. Randomization was carried out correctly and outcome assessors were blinded to the intervention provided insofar that the blinded participants filled the forms themselves. Outcome data was complete and participants adhered to the assigned intervention.</p> <p><i>Qualitative.</i> Adequate data collection methods and study design for the chosen research question. Findings are adequately and coherently derived, with interpretation substantiated by quotations.</p>	MH: nicotine dependence.	<p><u>dissolution</u> significantly correlated with the positive changes in behaviour and attitudes. Additionally, reappraisal of emotions was found to decrease the intensity of anxious ego-dissolution.</p> <p>Among the psilocybin-related factors which contributed to smoking cessation the researchers included “insights into self-identity (a different, deeper, better, more essential self)” and “<u>experiences of interconnectedness</u>”. The latter was experienced by 8 out of 12 participants and 6 of them were biologically confirmed as smoking-abstinent 12 months post-treatment. Of the 2 participants who were still smoking one never quit and reported a non-reduction in withdrawal symptoms. Another relapsed between 12-month and the long-term follow-up.</p>
Agin-Liebes et al., (2021a)	<p><i>Qualitative.</i> Appropriate design, data collection method and interpretation.</p>	MH: PTSD & complicated grief in relation to long-term AIDS.	<p>5 participants reported positive changes (less fear, anxiety, shame, guilt) due to “<u>acute phenomenological reductions in self-focus</u>”. These changes in turn enabled them to deepen their connection with others, communities, and the world and to experience more compassion, forgiveness, and gratitude – also towards themselves. For instance, one participant said his <u>ego-dissolution</u> experience made him refrain from self-judgement and that this made his anxiety fully disappear. Many participants experienced <u>connectedness</u> with other group members during the session and reported deriving a sense of emotional security from their connection which helped them process painful memories.</p>
Agin-Liebes et al., (2021b)	<p><i>Quantitative descriptive.</i> Relevant sampling strategy. Sample representative of White (83%) male (76%) psychedelic users from North America and Europe (60% and 20%, respectively). Appropriate measurements for the research goals. Only 477 out of 788 people who consented to</p>	<p>MH: depression, anxiety, AUD, DUD, PTSD.</p> <p>Wellbeing: changes in mood, attitudes, and behaviour.</p>	<p><u>Ego-dissolution</u> correlated with improvement across all measured conditions. It was the most significant for depression and anxiety ($P < 0.001$), very significant for drug use disorder ($P < 0.01$) and significant for alcohol use disorder ($P < 0.05$). The correlation with PTSD was found statistically</p> <p>(continued)</p>



Table 3. Continued

Author, date	Risk of bias appraisal	Primary MH/wellbeing outcome area	Results*
	participate completed the whole survey. Still, it was likely due to the large number of questionnaires rather than the dropouts being distinct. Hence, the nonresponse bias can still be considered low.		non-significant. In the final models (odds ratio), a greater intensity of insight was associated with increased odds of reporting improvement in all conditions but PTSD where mystical experience intensity was associated with symptom improvement. Almost all individuals whose psychological condition reportedly improved rated their mescaline experience as more personally meaningful, spiritually significant, and psychologically insightful than individuals who reported no improvement.

* References to ego-dissolution or connectedness are underlined.

Abbreviations: 5D-ASC – 5-Dimensional Altered States of Consciousness Rating Scale; ASC – Altered States of Consciousness (questionnaire); AUD – Alcohol Use Disorder; AWE-S – Awe Experience Scale; BSI-18 – Brief Symptom Inventory-18; DASS-21 – Depression Anxiety Stress Scale-21; DED – Dread of Ego Dissolution; DUD – Drug Use Disorder, EDI – Ego Dissolution Inventory; HRS – Hallucinogen Rating Scale; MEQ – Mystical Experience Questionnaire; MH – mental health; PCT – Picture Concept Test; PTSD – post-traumatic stress disorder; RCT – randomized controlled trial; SWL – Satisfaction With Life Scale.

on it exclusively, followed by two studies looking at the effects of ayahuasca, two investigating DMT and one researching mescaline. The remaining three studies were all surveys and looked at psychedelics in general. While [Kettner et al. \(2019\)](#) and [van Mulukom et al. \(2020\)](#) specified that they only included experiences induced by classic psychedelics, [Amada et al. \(2020\)](#) makes no mention of such a criterion. The paper was nevertheless included as the brief descriptive analyses section of the study indicates that LSD and psilocybin alone constituted 90% of the sample's early psychedelic experiences. Additionally, the qualitative part of the study's results only mentions different classic psychedelics and no non-classic ones.

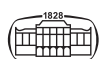
There was no apparent difference in the effectiveness of ego-dissolution and connectedness in improving wellbeing and mental health outcomes between the eight studies which investigated psychedelic use in naturalistic settings and the six studies where psychedelics were taken in a lab setting. However, [Kettner et al. \(2019\)](#) found that having the psychedelic experience in the natural environment had a significant influence on the outcome. It was the only study to compare outcomes after outdoors and indoors experiences. Moreover, it would likely be informative to replicate the unique setting of five-day mindfulness retreats in [Smigielski et al. \(2019\)](#) as the paper report particularly persistent long-term effects of ego-dissolution.

Population. Most of the participants were White and from Western anglophone countries – United Kingdom, United States and Canada – and some European countries.

Two studies represent exceptions from this demographic norm: [Uthaug et al. \(2018\)](#) where half of the sample was recruited in Colombia and [Argento et al. \(2019\)](#) where the psychedelic treatment was offered to members of a specific indigenous community only. Coincidentally, these more ethnically diverse studies are at the same time the only two ayahuasca studies in the review, with the psychedelic session being ceremonial in both cases. This might confound any possible effects of either ethnicity or ceremonial ayahuasca experience on the outcome.

While the studies included participants from age groups above the age of 18 and from various educational and employment backgrounds, the majority of the samples were predominantly male. This might be partially due to the recruitment means in the case of online surveys which sought participants through websites such as Reddit with a largely male user base ([Duggan & Smith, 2013](#)). Still, given the persistence of the gender bias across surveys, it is also possible that the samples' composition is reflective of an actual gender ratio among the psychedelic users. Regardless, none of the included studies reported a difference in the effects of ego-dissolution or connectedness on mental health or wellbeing based on gender, and no such difference was detectable in the analysis of individual participants' data.

Finally, the studies' results were analysed to see whether previous experience with psychedelic substances correlated with higher or lower effect of ego-dissolution or connectedness on psychological outcomes. One study, [Uthaug et al. \(2018\)](#), carried out an analysis to investigate this issue and reported directly that the subacute effects of ayahuasca did



not differ depending on participants' previous experience with the brew (acute effects were not investigated in the study). No study reported a correlation between past psychedelic experience and psychological outcomes following the most recent psychedelic session.

Ego-dissolution, connectedness, and psychological outcomes. Immediate therapeutic effect of ego-dissolution on the study's outcome area was reported by seven studies (Agin-Liebes, Ekman, et al., 2021; Amada et al., 2020; Nielson et al., 2018; Smigielski et al., 2019; Uthaug et al., 2018, 2019, 2020), four out of which reported the correlations between ego-dissolution and their outcomes sustained in the long-term (subjectively perceived positive psychological changes in Amada et al., 2020; alcohol use in Nielson et al., 2018; changes in behaviour and attitudes in Smigielski et al., 2019; the non-reactivity facet of mindfulness in Uthaug et al., 2018). Nevertheless, despite the lasting association between ego-dissolution and non-reactivity at 4-weeks follow-up reported in Uthaug et al. (2018), five other associations present immediately after the psychedelic experience were no longer statistically significant at this later timepoint. Uthaug et al. (2020) employed a shorter, 7-day follow-up and found all the psychological outcomes to still be affected at this time point, with the correlation between ego-dissolution and anxiety becoming even more significant. Two studies, Kettner et al. (2019) and Agin-Liebes et al. (2021b), found an indirect effect of ego-dissolution on psychological improvement, mediated by nature-relatedness and psychological insight, respectively.

Ego-dissolution did not correlate with the measured psychological outcome to some extent in five studies, most profoundly in van Mulukom et al. (2020), where there was no association between the levels of maladaptive narcissism and ego-dissolution at all. Whilst Agin-Liebes et al. (2021b) found a correlation between ego-dissolution and decreased symptoms of other mental health conditions, there was no correlation with post-traumatic stress disorder (PTSD). In the other three studies, it was only at follow-up that the effect was found to have waned (Uthaug et al., 2018, 2019) or was reported only by one out of nine participants (Agin-Liebes et al., 2021a). Anxious ego-dissolution (or dread of ego-dissolution) was investigated in two papers and in both it was found to correlate with negative psychological outcomes (Roseman et al., 2018; Uthaug et al., 2020).

Different types of connectedness were reported across the included papers, usually several kinds within a study. Thus, a sense of unity with others during the experience was mentioned in four papers (Agin-Liebes, Ekman, et al., 2021; Amada et al., 2020; Belser et al., 2017; Watts et al., 2017). Among them, Agin-Liebes, Ekman, et al. (2021) was the only study where the psychedelic sessions were carried out in group setting which enabled the experience of connectedness with other cohort members. Additionally, connectedness with nature was reported in four papers (Argento et al., 2019; Amada et al., 2020; Belser et al., 2017; Watts et al., 2017). The most commonly reported kind of connectedness was connection with Spirit/All, alternatively referred to as:

“that bigger ultimate place to be” (Nielson et al., 2018), the universe (Agin-Liebes, Ekman, et al., 2021; Amada et al., 2020; Noorani et al., 2018; Watts et al., 2017), God (Watts et al., 2017), “a great plane of consciousness” (Belser et al., 2017), etc., or described as a sense of connection to everything in the world. This kind of connectedness featured in seven studies (Agin-Liebes, Ekman, et al., 2021; Amada et al., 2020; Argento et al., 2019; Belser et al., 2017; Nielson et al., 2018; Noorani et al., 2018; Watts et al., 2017), which also happened to be all the studies in the review that incorporated a qualitative element. Additionally, connectedness was experienced as love by certain participants in two studies (Amada et al., 2020; Noorani et al., 2018) and was described as a tool for resolving trauma in two others (Agin-Liebes, Ekman, et al., 2021; Watts et al., 2017).

An immediate therapeutic effect of connectedness was found in ten studies (Agin-Liebes, Ekman, et al., 2021; Amada et al., 2020; Argento et al., 2019; Belser et al., 2017; Nielson et al., 2018; Noorani et al., 2018; Uthaug et al., 2019, 2020; Watts et al., 2017) and a long-term therapeutic effect, from five weeks to 30 months to an unspecified timeframe in retrospective surveys, was established in eight studies (Amada et al., 2020; Argento et al., 2019; Belser et al., 2017; Nielson et al., 2018; Noorani et al., 2018; van Mulukom, et al., 2020; Roseman et al., 2018; Watts et al., 2017). Connectedness did not correlate with a psychological outcome in three studies – Uthaug et al., 2019 (at 4-weeks follow-up), Noorani et al., 2018 (for two participants), and for the same single participant in Agin-Liebes, Ekman, et al. (2021) mentioned above as not improving despite ego-dissolution. In Uthaug et al. (2020) the positive correlation between the measure of oceanic boundlessness and non-judgement became more significant at the 7-day follow-up, while the positive correlation with satisfaction with life and the negative correlation with depression lost their significance at this timepoint. Connectedness correlated with improvement on at least one measure of mental health or wellbeing in all the studies included in this review.

Subgroup analysis: outcome domains. The last analysis carried out focused on the therapeutic effectiveness of ego-dissolution and connectedness within different outcome domains. Firstly, many studies did not investigate improvement within clinical categories, but rather through ratings and descriptions of participants' wellbeing, stress reduction, quality of and satisfaction with life, psychosocial functioning or trait and state mindfulness. There were nine studies that reported on one or more of these outcomes, out of which six found a positive correlation between ego-dissolution and wellbeing (Amada et al., 2020; Kettner et al., 2019; Smigielski et al., 2019; Uthaug et al., 2018; Uthaug et al., 2018, 2018, 2019, 2019, 2020, 2020; Watts et al., 2017) and six found a positive correlation between connectedness and wellbeing (Amada et al., 2020; Argento et al., 2019; Belser et al., 2017; Uthaug et al., 2019, 2020; Watts et al., 2017). No study found a negative correlation either with ego-dissolution or connectedness. The effect of ego-dissolution on wellbeing was found to be limited in Uthaug et al. (2019),



where the correlation diminished to non-significant levels in majority of categories after 4 weeks.

Depression was the second most frequently researched domain with six studies reporting on the outcome, followed by anxiety with five studies. Ego-dissolution was found to negatively correlate with depression in four studies (Agin-Liebes et al., 2021b; Uthaug et al., 2018, 2019, 2020) and with anxiety in four studies, too (Agin-Liebes et al., 2021b; Belser et al., 2017; Uthaug et al., 2019, 2020). Out of the latter subgroup, Belser et al. (2017) focused on anxiety related to cancer diagnosis and found that dissolution of self as well as experiences of interconnectedness had a lasting positive impact on the participants' mental health. While Uthaug et al. (2018) measured anxiety as well, due to very low baseline levels of anxiety in the sample, the observed reduction in the scores post-session was statistically non-significant.

Three studies looked at the relationship between connectedness and depression. Uthaug et al. (2020) found oceanic boundlessness to negatively correlate with depression immediately after the 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) session, with the correlation rendered insignificant by the 7-day follow-up. Watts et al. (2017) found lasting improvement in previously depressed participants, while Roseman et al. (2018) found the measure of OBN to predict improvement in depressive symptoms for at least 5 weeks post-session. A "complete" OBN (>0.6) was associated with better scores for secondary clinical outcomes like trait anxiety, anhedonia, optimism, or pessimism.

Four studies investigated the effectiveness of psychedelic therapy in treating addiction. Noorani et al. (2018) found that out of eight individuals who reported experiencing "interconnectedness" seven stopped smoking, with one person relapsing after the 12-month follow-up. Two studies focused on alcohol dependence, Agin-Liebes et al. (2021b) and Nielson et al. (2018). The former study showed that out of four participants who experienced a 100% reduction in heavy drinking days, two described experiencing radical changes to the sense of self during the sessions, which included the sense of loss of self as well as oneness, and which correlated with high Mystical Experience Questionnaire (MEQ) scores. Meanwhile, the latter study showed that ego-dissolution significantly correlated with reduction in alcohol misuse, but the association with drug misuse score was even more significant. Lastly, the interviews carried out by Argento et al. (2019) suggest that connectedness was common and had a positive impact on the wellbeing of substance-dependent participants.

Individuals with PTSD participated in two studies by Agin-Liebes et al. (2021a, 2021b). The first paper focused solely on males with long-term AIDS (AIDS), PTSD, and complicated grief. The interviews with this sample revealed ego-dissolution in particular to have had profoundly positive effects on the participants' mental state, while the experience of connectedness with other group therapy members during the psilocybin session was a source of significant emotional support. Yet, the second study, a mescaline-focused survey, found PTSD to be the only

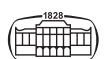
condition measured that did not show a significant negative correlation with ego-dissolution.

The last clinical category considered in the included studies was maladaptive narcissism (van Mulukom et al., 2020). The retrospective survey did not find an association between present levels of maladaptive narcissism and past experience of ego-dissolution, but did find a negative correlation between connectedness and exploitative-entitled narcissism. However, this correlation was only true in the case of connectedness towards nature or humanity, but not connectedness to the universe at large.

Subgroup analysis: ego-dissolution vs connectedness. Quantitative studies found both ego-dissolution and connectedness to significantly correlate with improvements in mental health and psychological wellbeing outcomes. However, it seems that effects of connectedness tend to be more long-lasting, while ego-dissolution correlates with short-term rather than long-term changes. Only three studies found sustained effects of ego-dissolution: on alcohol consumption reduction at least until 4 weeks after the second psilocybin session in Nielson et al. (2018); on enabling a positive, permanent transformation of self in Amada et al. (2020) and on positive behavioural and attitudinal changes in Smigielski et al. (2019) at 4-month follow-up. In Uthaug et al. (2018) only one correlation out of the six detected immediately after the ayahuasca ceremony was still present at the 4-week follow-up, while Uthaug et al. (2019) found no correlations between ego-dissolution and any of the measured outcomes 4 weeks after a 5-MeO-DMT session.

A notion repeated throughout a number of studies is that ego-dissolution might act more as an intermediary enabling therapeutic action, rather than as a remedy in itself. The experience was described as a tool for gaining an objective, outside perspective on one's own self and life in four different studies: Agin-Liebes et al. (2021a, 2021b), Amada et al. (2020), Nielson et al. (2018). In the last study, mescaline-induced ego-dissolution was originally found to correlate with improved outcomes for depression, anxiety, alcohol, and drug use disorders. When an odds ratio analysis was run, however, it was found that after controlling for ego-dissolution and mystical experiences, only psychological insight was significantly predictive of improvements in these groups. These findings suggest that while experiencing ego-dissolution is associated with more positive mental health changes, it might be due to the larger number or greater profundity of psychological insights it enables.

Connectedness might differ from ego-dissolution in two ways – immediate psychological impact and duration of the state. Firstly, the reviewed studies indicated that connectedness, but not ego-dissolution, can be partially sustained following the psychedelic experience, thus in itself translating to a positive psychological outcome. Only Uthaug et al. (2020) found a clear lack of correlation between connectedness and wellbeing at 4-week follow-up, with two other studies (Agin-Liebes et al., 2021a; Noorani et al., 2018) having mixed results. On the other hand, eight studies found an association between connectedness and positive



long-term outcomes. One participant in [Belser et al. \(2017\)](#), for instance, claimed that her life-long sense of loneliness disappeared after the session, replaced by a sense of “global connectedness” revealed to her during the psychedelic experience.

Secondly, unlike ego-dissolution, connectedness is related to several feelings that might be therapeutic to individuals: love, belonging, compassion, consolation, comfort. [Watts et al. \(2017\)](#) includes an account of an individual who was severely abused in childhood, but who managed to address the trauma of the event through connectedness and compassion. Similarly, [Agin-Liebes et al. \(2021a\)](#) mentions that two participants experienced the resentment they held towards family members or partners being transformed into acceptance, forgiveness, and gratitude, which affected their relationships positively after the session. Meanwhile, [Noorani et al. \(2018\)](#) quoted one of their participants saying she experienced a feeling of unitive love towards everything which stayed with her to some degree after the psilocybin session and helped in reducing her nicotine consumption: “Love is a pretty big distraction from addiction and [...] my attention kept going back to it, that great feeling of love and acceptance”.

Weight of evidence assessment

The 15 studies presented here provide a good indication of effects of both ego-dissolution and connectedness on mental health and wellbeing, while at the same time showcasing possible differences between the two phenomena. While effects found in individual studies could be exaggerated due to issues mentioned in the risk of bias assessment, the affinity of findings reached using very diverse methodologies adds reliability to the overall synthesised result of the review.

Conclusions about the likely size and direction of effect. Ego-dissolution and connectedness were found to be significant factors in psychological improvement following a psychedelic experience. Although experiencing either (or both) of them does not guarantee a mental health recovery or wellbeing improvement, they appear to be strongly correlated with psychological improvement. Their effectiveness might depend on the condition investigated, individual characteristics, context of the experience and form of integration.

Applicability to different population groups and/or contexts. Most research was carried out in White and Western anglophone populations. The findings of the two more diverse studies in the review suggest that the effects could be applicable to other populations, but this indication is far from conclusive. Much more research should be carried out in various cultural settings in order to validate the applicability of these results to other populations.

DISCUSSION

The present systematic review aimed to investigate the impact of ego-dissolution and connectedness on therapeutic

effects of the psychedelic experience. This was done by the means of narrative synthesis of 15 studies. As a result of this research, ego-dissolution and connectedness were found to consistently correlate with improvements in mental health and wellbeing, which is in line with the main hypothesis of the review. Additionally, the findings indicate that ego-dissolution and connectedness, while often related, are not necessarily two aspects of the same psychological event. This contradicts the secondary hypothesis of this review – that ego-dissolution and connectedness are correlated as part of the same phenomenon – and brings a perspective so far absent from the psychedelic therapy debate. A statistical analysis carried out by [Uthaug et al. \(2019\)](#), one of the included studies, further strengthens this notion, showing that EDI and OBN scores of their participants were not correlated. The reports from interviewees in qualitative studies such as [Nielson et al. \(2018\)](#) or [Agin-Liebes et al. \(2021a\)](#) suggest that ego-dissolution functions predominantly as a tool for reshaping one’s self from a detached standpoint. Feelings such as guilt and shame, associated with self-identity in a non-altered state of mind, might be let go through ego-dissolution. In their place more psychologically beneficial associations can be formed, improving the person’s self-image and worldview.

Connectedness, on the other hand, might be in itself a therapeutic experience. While ego-dissolution does not continue past the psychedelic experience, participants of the included studies frequently mentioned experiencing connectedness – and the associated feelings of belonging ([Belser et al., 2017](#)), love ([Noorani et al., 2018](#)), responsibility for others ([Amada et al., 2020](#); [Noorani et al., 2018](#)) – for days or weeks following the psychedelic session. Moreover, where ego-dissolution triggers changes to one’s self-perception, connectedness might be more beneficial in healing interpersonal relationships. It was the experience of connectedness that led some participants to improve their relationship with their loved ones ([Agin-Liebes et al., 2021a](#); [Belser et al., 2017](#)) and it was connectedness-induced compassion that helped a participant in [Watts et al. \(2017\)](#) process his childhood trauma. This line of understanding accounts also for the finding that connectedness but not ego-dissolution is associated with lower levels of maladaptive narcissism.

This review’s results are consistent with recent findings that ego-dissolution correlates with improvement in wellbeing ([Nour et al., 2016](#)) and with a study by [Carhart-Harris et al. \(2016\)](#) where the experience of a psychedelic-induced unitive, spiritual, and blissful state predicted the reduction of participants’ depressive symptoms. Likewise, the present study is in line with [Letheby’s \(2021\)](#) argument that the beneficial effects of psychedelic therapy are achieved through “changes to the sense of self” induced by, among other factors, ego-dissolution and connectedness. In summary, previous literature and this review support the notion that connectedness is one of the key elements driving the efficacy of psychedelic therapy, as argued by [Carhart-Harris et al. \(2018\)](#).

Furthermore, the presented results align with non-psychedelic research on mental health. For instance, loneliness,



which can be understood as the lack of connectedness, has been established to be a risk factor for depression (Cacioppo et al., 2006), and being depressed can in turn increase the sense of loneliness (Lalayants and Prince, 2015). Similarly, in alcohol dependence perceived loneliness was found to be both a predictor for developing the condition, and an obstacle to recovery (Åkerlind & Hörnquist, 1992). More generally, a low sense of social belonging has been associated with lower psychological functioning, including higher incidence of anxiety and suicidality (Hagerty et al., 1996). Given the role loneliness and lack of social belonging have in a variety of mental health problems, it is not surprising that the experience of connectedness could have the reverse effect.

Similarly, there is a theoretical basis for ego-dissolution's therapeutic effectiveness in non-psychedelic literature. Firstly, a meta-analysis of 226 effect sizes (Mor & Winquist, 2002) found self-focused attention to be associated with negative affect, particularly in clinical and female samples and when combined with rumination. Experiencing selfless cognition by definition interrupts this mental habit, as found by Orłowski et al. (2022). Moreover, negative self-perception has long been theorized to underlie some of the mental health problems (Beck, 1976), something ego-dissolution challenges by stripping away self-judgement (Amada et al., 2020), increasing self-compassion (Stansbury, 2019), and reducing public self-consciousness (Orłowski et al., 2022). Lastly, most of the participants in this review come from societies characterized by individualism, where mental health is considered a matter of one's own responsibility and resilience (Garrett, 2016; Zilberstein, 2021). As a result, mental health problems can be associated with self-blame and shame, responses that ego-dissolution can detach the psychedelic user from.

Limitations and future directions

The defining characteristic of this systematic review is the heterogeneity of the studies included which, while enriching, also limits the scope of possible analysis. Most of the studies were methodologically unique and so, while it was possible to synthesise their results based on common themes, many study characteristics could not be sufficiently analysed. Moreover, separate mental health conditions or aspects of wellbeing could not be analysed in all their complexity due to the heterogeneity of the review's comparator.

Investigating phenomena like ego-dissolution or connectedness is challenging due to the ambiguity between subjective states one might go through during a psychedelic experience. While one study included in the review concluded that ego-dissolution and connectedness do not correlate with each other, it could be contested by some whether it is possible to quantify, separate or even describe accurately the experiences so often referred to as ineffable (Breksema et al., 2020; McKenna, 1991). Moreover, ego-dissolution and connectedness are not only related to each other, but also to mystical, awe, and psychological insight experiences (Barrett & Griffiths, 2018; Hendricks, 2018).

Since one of the included studies found psychological insight to be the determining factor for the improvement of the majority of the participants, it would be worthwhile to replicate the analysis in other samples and settings in the future to see whether this finding can be validated. The newly developed PIS-6 tool (Peill et al., 2022) promises more future research will be dedicated to the role of psychological insight in psychedelic experience.

Yet, these experiences often co-occur during the peak of the psychedelic experience and decoupling them might have little practical use in psychedelic therapy. This is reflected in the overlap visible in quantitative measures such as the Mystical Experience Questionnaire (Barrett, Johnson, & Griffiths, 2015) with items investigating "sense of awe or awesomeness" and "experience of amazement". In the present review too, many of the experiences of connectedness and ego-dissolution described by participants had clear signs of being mystical, awe-inducing or insight-revealing. The impossibility of clearly separating these experiences through analysis might be considered a limitation of the review, even if an inevitable one.

The primary area for which the above findings may be applied is psychedelic therapy, the effectiveness of which may be increased by placing the right emphasis on ego-dissolution and connectedness. Despite the potential of ego-dissolution to facilitate positive psychological change, anxious ego-dissolution has been connected to negative outcomes. Hence, research should be carried out to determine the factors that enable individuals to enter ego-dissolution without fear. Preliminary findings suggest that traits of preoccupation, confusion, and apprehension are positively correlated with anxious ego-dissolution, while openness was found to be negatively correlated (Russ et al., 2019). Thus, future pre-session preparation techniques might be based on reduction of worry and promotion of openness.

Moreover, since the effects of ego-dissolution on psychological outcomes appear to be more short-lived than those of connectedness, research could be carried out to investigate what could prolong the mental health and well-being benefits of the former psychedelic state. Lastly, the hypothesis that ego-dissolution mediates more directly therapeutic experiences (such as connectedness, psychological insight, etc.) could be tested through mediation analysis.

As connectedness was found to often last longer than other psychedelic effects, this experience could be particularly emphasised during integration. One aspect to consider at the post-session stage is how connectedness may increase feelings of responsibility for others, society, and environment (Amada et al., 2020). Through exploration and encouragement of these feelings individuals' psychological functioning could be further improved, with chances of more sustained effect (Santini et al., 2018). Moreover, given the findings discussed in the review which suggest a positive feedback loop between nature-relatedness and wellbeing (Kettner et al., 2019), increased exposure to nature could be explored by individuals who experienced nature connectedness. Lastly, in order to prevent socially isolated individuals from relapsing into feelings of loneliness after the



session, the connectedness-induced sense of belonging and social engagement could be supported through engagement in local communities and group meetings.

The relationship between context, psychological predispositions, and the observed effects of ego-dissolution and connectedness should be investigated in future research. For instance, one included study which reported long-term positive effects of ego-dissolution on wellbeing had a very specific design of a several days long Zen meditation retreat with a sample of experienced meditators. It would be informative to investigate the effects of both mindfulness meditation experience and the structured, retreat setting on the effects of ego-dissolution as well as connectedness or psychedelic therapy in general.

Relatedly, there is still no clear model of integration that could be referred to in literature. For the studies included in the review, the ambiguity on the details of post-session psychotherapy made it impossible to analyse the mediating effects of different kinds of integration on the relationships between ego-dissolution and connectedness and psychological outcomes. Therefore, more dedicated investigation and reporting of different integration techniques would be beneficial to this area of research and, consequently, would lead to more effective practice in the future.

Nevertheless, the findings of this review are also of relevance to the wider mental health context. While it is unrealistic to attempt to treat all mental health problems with psychedelic therapy, given the therapeutic potential of ego-dissolution and connectedness, equivalent non-psychedelic experiences could be emphasized in other modes of therapy as well as in daily life. Nature-relatedness achieved through contact with nature (Fretwell & Greig, 2019) and social prescribing (Kimberlee, 2013; Polley, Seers, & Fixsen, 2019) have both been found to be beneficial for mental health and psychological wellbeing. Mindfulness-based therapies like mindfulness-based cognitive therapy or acceptance and commitment therapy can be considered less intense equivalents of ego-dissolution insofar as they reduce self-focused cognition (Gu et al., 2015; Hayes, Strosahl, & Wilson, 1999). All these means of therapy could be proposed as alternatives to psychedelic therapy in light of the review's findings.

Conclusion

Ego-dissolution and connectedness were found to potentiate the therapeutic effects of psychedelic experience by promoting improvement in psychological wellbeing across several mental health conditions, particularly depression, anxiety, and substance use disorders. Given the significant heterogeneity of research within this nascent area, questions on the possible mediating effect of specific elements of study design like physical context or integration remain open. However, the present review was able to identify several key differences between ego-dissolution and connectedness which may be utilized for further theory-building and creation of psychedelic therapy models. Finally, the therapeutic efficacy of ego-dissolution and connectedness suggests their reverse manifestation – overly self-focused cognition and

perceived isolation – might be underlying factors for much of mental suffering. Thus, the review's findings have implications beyond the psychedelic research field alone and are applicable to the general mental health debate.

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Appendix

((connectedness or interconnectedness or oneness or “unitive-experience*” or “oceanic boundlessness” or (“ego-death” or ego-dissolution or ego-loss or ego-disintegration or self-loss or self-dissolution or “loss-of-self” or ego-consciousness or “identity loss” or “identity dissolution” or “self-referential awareness” or “self-construal” or egocide)) and (entheogen* or hallucinogen* or psychedelic or psychoactive or psychotomimetic or psychotropic or serotonergic or

serotonin-agonist* or 5-hydroxytryptamine agonist* or 5-HT agonist* or indole* or tryptamine* or psilocin* or 4-HO-DMT or psilocybin* or 4-PO-DMT or bufotenin* or 5-HO-DMT or 5-MeO-DMT or DMT or N,N-Dimethyltryptamine or ayahuasca or ergoline* or lysergamide* or “lysergic acid diethylamide” or LSD or “lysergic acid amide” or ergine or LSA or ergot or Claviceps or phenethylamine* or mescaline or peyote or San Pedro or lophophine or ibogaine))

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