The Psychological Processes of Classic Psychedelics in the Treatment of Depression: A Systematic Review Protocol

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Protocol

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Abstract

Background

There is currently renewed interest in the use of psychedelic therapy in the treatment of psychiatric disorders, including depression. The proposed systematic review will aim to identify, evaluate and summarise the psychological processes of change underlying psychedelic therapy for depression in the current literature and consider the implications these processes may have on the psychotherapy component of treatment.

Methods

Scopus, PsycINFO, PubMed and Web of Science databases will be searched using relevant terms. Studies will be included if they discuss the use of a classic psychedelic to treat depression symptomology in an adult population and report or propose psychological processes responsible for depression symptom change. Two authors will independently screen articles, complete quality assessment tools and conduct data extraction. Empirical and non-empirical research will be extracted and synthesised separately. A narrative synthesis approach will be used to report psychological processes identified in the literature.

Discussion

This systematic review will be the first to collate available evidence on the psychological processes associated with psychedelic therapy for depression. The preliminary nature of this research field is expected to result in the review having several limitations, namely heterogeneity between studies and a lack of empirical research. We intend for this review to present the current state of the literature, identify gaps and generate candidate variables that warrant further investigation.

Systematic Review Registration

PROSPERO CRD42020197202

Background

Classic psychedelics are a group of psychoactive drugs that includes lysergic acid diethylamide (LSD), psilocybin, N,N-dimethyltryptamine (DMT) and mescaline (1). When ingested, these compounds can elicit altered states of perception, cognition and emotion (2). Despite having distinct characteristics, the classic psychedelic compounds are often grouped together as they all act as agonists for serotonin 5-hydroxytryptamine (5-HT) 2A receptors (3). It is through this receptor agonism that classic psychedelics primarily exert their psychoactive effects (1).

The use of the classic psychedelics by non-Western cultures can be traced back thousands of years. The sacramental consumption of mescaline, via ingestion of the Peyote cactus (*Lophophora williamsii*), has occurred in Native American ceremonies for at least 5 millennia (4), and there is evidence to suggest that
DMT-containing plants have been ingested by some in South America since 2130 BC (5). Similarly, psilocybin-containing mushrooms may have been used in Mesoamerican ceremonies for 3500 years (6).

The clinical use of psychedelics first sparked interest in modern Western medicine in the 1940s (2), when LSD was first synthesised and ingested (7). This discovery sparked numerous studies into the use of the classic psychedelics (namely LSD and psilocybin) in the treatment of psychiatric disorders. However, political motivations in the beginning of the 1970s caused an abrupt end to this era, when known psychedelics were prohibited under the Controlled Substances Act (8). A 20 year research hiatus followed (9), until several studies in healthy participants gained ethics approval (10-13) through utilising psychedelics with less notoriety than LSD. This paved the way for research to slowly recommence.

**Classic Psychedelics and Depression**

Since research has resumed, promising results have been reported on the clinical benefits of classic psychedelics across a range of psychiatric disorders, including depression (14). Several trials have reported psilocybin to produce significant and long-lasting improvements for those with treatment resistant depression (15, 16) and depression associated with life threatening cancer (17, 18). Similar reductions in depression symptoms have been described with ayahuasca, a brew containing DMT from the *Psychotria viridis* plant and monoamine oxidase inhibitors from the *Banisteriopsis caapi* vine (19-21).

In fact, recent systematic reviews have reported significant, rapid and sustained reductions in depressive symptoms in all modern trials which utilise either psilocybin or ayahuasca (22, 23). Psychedelic therapy offers several advantages over conventional anti-depressant treatment. Most notably, psychedelic therapy appears to produce greater reductions in depression symptoms when compared to typical pharmacological and psychological treatments (24). These symptom changes typically result from a short treatment program and usually occur immediately following treatment, unlike the weeks or months typically seen in current treatments (25). Reductions in depression symptomology appear to be well sustained post-treatment (15), yet additional longitudinal outcomes are needed to corroborate this.

Exactly how classic psychedelics work to reduce depression symptoms is still largely unknown, although several potential mechanisms have been proposed. Increased functional connectivity within the default mode network (DMN), a group of brain regions which show increased activity during rest and decreased activity during cognitively demanding tasks as well as decreased functional connectivity between executive networks and the DMN, has been associated with the pathophysiology of major depressive disorder (26, 27). A number of studies have now shown that classic psychedelics reduce activity and internal functional connectivity within the DMN, potentially reducing abstracted (perceptually-decoupled) and self-referential rumination, a hallmark of depressotypic thinking (22, 28). Moreover, there is now evidence to suggest that the psychedelic state produces co-activation between the DMN and task positive networks (a network of brain regions which activate during attention demanding tasks), two networks which are usually anti-correlated (29). It is possible that this co-activation may be contributing to the novel experiences and outcomes which occur during psychedelic therapy (29). Several other neurological...
mechanisms of action have been proposed. Alterations in amygdala reactivity to emotional stimuli (30-32), increased concentrations of glutamate and brain-derived neurotrophic factor (33, 34) and reductions in inflammatory agents (35) have been suggested to contribute to the antidepressant effects of psychedelics, with varying degrees of evidence. However, more research is required to comprehensively understand how psychedelics may be acting on the brain to alleviate depressive symptoms.

**Set and Setting: Psychological Processes in Psychedelic Treatment**

It is important to note that the context in which classic psychedelics are used requires significantly greater consideration than traditional depression pharmacotherapies. This is due to both the positive therapeutic effects of the interpersonal context in which consumption takes place (36), as well as a number of risks associated with psychedelic consumption. These risks include transient anxiety, panic and, very rarely, prolonged psychosis (37). It has long been recognised that both *set* (the mindset of the participant, including their expectations, assumptions and intentions for the psychedelic experience, as well as stable variables such as personality and the presence of psychopathology) and *setting* (the physical, social and cultural environment in which the experience occurs) have the potential to greatly impact the outcomes of the psychedelic experience (38, 39). *Psychedelic-assisted psychotherapy* aims to account for this by conducting psychotherapy with participants (usually in addition to the psychedelic consumption) in order to ensure participants approach psychedelic therapy with a suitable set. Participants take part in several sessions of psychotherapy before their psychedelic session, which act to set constructive expectations and intentions for the experience (37). Additional sessions are provided following the psychedelic session, to assist in integrating their psychedelic experience once it is complete (40). Contemporary clinical trials have also addressed setting, by providing a comfortable and aesthetic environment, in addition to music and eye masks, for the psychedelic session to take place (37). During these dosing sessions, a non-directive therapeutic style is adopted, with therapists instructing participants to ‘focus inward’ (41). They may also provide support or encouragement for participants to engage with any challenging thoughts or memories that emerge (41).

As indicated by the above procedures, the psychological and social context in which psychedelic-assisted psychotherapy occurs is of particular importance. This raises questions regarding the potential psychological process which may be contributing to changes in depression symptoms. A focal point of this research area to date has been investigating mystical-type experiences, which includes the occurrence of “profound unity with all that exists, a felt sense of sacredness [and] a sense of the experience of truth and reality at a fundamental level” (13). This experience is often operationalised into four factors; mysticism (a sense of unity, sacredness and noetic quality), positive mood, transcendence of time and space, and ineffability (difficulty in describing the experience; 41). Undergoing a mystical experience has been associated with positive wellbeing in healthy volunteers (43, 44), and reductions in depression symptoms in participants with life-threatening cancer (18, 45). Others have reported significant increases in the personality traits openness and extraversion, along with decreases in
neuroticism, following therapy (46, 47). Additional psychological variables which have been suggested to be involved include increased emotional connectedness and acceptance (48), greater psychological flexibility (49) and experiencing an emotional breakthrough during dosing (50).

However, little is currently known about the importance of these, and other potential psychological mechanisms involved in psychedelic-assisted psychotherapy for depression. Given the importance of the psychological and social context in the delivery of this treatment, knowledge advancement in this area has the potential to strengthen treatment outcomes and minimise associated risks. A greater understanding of the underlying psychological processes may allow for treatment protocols to be refined, ensuring the most effective and safe treatment is delivered. One method of advancing our understanding is to conduct a thorough systematic review of the current literature, to collate evidence, uncover gaps in the literature, and facilitate future research. Therefore, the overarching aim of this systematic review will be to identify how classic psychedelics may operate at the psychological level to improve depression symptoms. The review will address two main questions: (i) what psychological processes of psychedelic therapy for depression symptoms can be discerned in existing literature, and (ii) what implications do proposed psychological processes have for the psychotherapy component of psychedelic-assisted psychotherapy?

**Methods**

The systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/PROSPERO, registration number: CRD42020197202). It will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) recommendations for systematic review protocols (51) and findings will be reported in accordance to PRISMA guidelines (52).

**Criteria for Study Inclusion**

**Study Methods**

All study methods, including experimental designs, reviews, theoretical and conceptual analyses, will be sought. It is recognised that broadening the inclusion criteria to allow all levels of knowledge may reduce the quality of evidence included in the review. However, as this is an emerging field, it is anticipated that there will be few randomised controlled trials or open label studies. We aim to offset these concerns by conducting separate data extraction forms and synthesis for empirical and non-empirical data. Included articles must be published in a peer-reviewed journal.

**Population**

To be eligible for inclusion, empirical studies must collect data on adults with depressive symptoms. A variety of symptom measurement approaches will be accepted (e.g. self-report, standardised measures, interviews) and the psychometrics of the approach will be considered when reporting outcomes. Studies
which include participants with co-occurring mental disorders or symptoms will be included. Data extraction and synthesis will occur separately for studies where depression symptomology is the primary focus of the research and those which consider other disorders or symptoms to be their primary outcome.

**Intervention**

Studies must report on or discuss the use of a classic psychedelic (LSD, psilocybin, DMT/ayahuasca or mescaline) in treating depression symptoms. To focus the review, only papers considering high dosages of psychedelics will be included. Whilst this review aims to uncover psychological mechanism of action, studies will be included even where the tested intervention did not include adjunctive psychotherapy or emotional support, as meaningful data/commentary on psychological mechanisms of psychedelics may be provided.

**Outcomes**

To be included in the review, studies must report on or propose psychological processes of psychedelic therapy in the treatment of depression. We expect that such variables may be identified from a range of sources in the literature, including statistical analysis, qualitative interviews or inferences from theoretical analysis.

**Procedures**

**Search Strategy**

Scopus, PsycINFO, PubMed and Web of Science databases will be searched to identify potential studies. The search will be restricted to only include publications from 1990 to present, so to focus on the recent period of psychedelic research. Following screening, a search for potentially suitable but uncaptured articles will be run through a backward search of the reference list of included articles, as well as a forward search of articles which have cited the selected articles. Database searches will be saved, and alerts will be used to notify authors of the publication of new articles which match the searches. An example of the search strategy to be used for Scopus can be found in Table 1.

**Study Selection**

Identified articles will be collated into Rayyan (53) and duplicates removed. Article selection will be completed by two reviewers (LJ and LMP) and take place in two steps. The first stage will involve titles and abstracts being screened against inclusion and exclusion criteria. In the second stage, the results from each reviewer's study selection will be compared. Full texts will be reviewed if discrepancies occur, and Cohen's Kappa for inter-rater reliability will be assessed and reported. A third reviewer (GM) will make the final decision if agreement cannot be reached.

**Data Extraction**
Data extraction will be completed independently by two reviewers (LJ and LMP) using Excel spreadsheets. Both reviewers will pilot these forms on five studies initially, with amendments being made after this if necessary. As substantial heterogeneity is expected between studies, included studies will be categorised into three distinct groups, each with an individual data extraction form. These groups will be: empirical research where depression symptomology is the primary target, empirical research where symptomology other than depression is the primary target, and non-empirical research. Data to be extracted from the empirical studies will include participant demographic information, sample size, type and severity of depression, method of measuring depression symptoms, other diagnosis/symptomology, study design and methodology, psychedelic used, outcome data (e.g. changes in depression) and psychological processes. The form for non-empirical work will focus on proposed psychological processes and the theory or evidence cited to support these variables.

Both reviewers will then conduct quality assessments on each article. A modified version of Murad and colleague's methodological quality assessment tool will be used to assess quantitative studies (54). This tool examines the quality of participant selection methods, ascertainment of exposure and outcomes, how causality was determined and the reporting of outcomes. Qualitative studies will be appraised using Dixon-Woods and colleague's tool for appraising qualitative research (55). This instrument examines the clarity of research questions, methodology and data integration, the suitability of the qualitative methodology used to answer the research questions, as well as the appropriateness of the conclusions drawn. If an agreement on the quality of an article cannot be reached, a third reviewer (GM) will be used. Non-empirical studies and reviews will not be included in the quality assessment process, however outcomes produced from these designs will be considered during data synthesis.

**Data Synthesis**

A narrative synthesis of selected articles will be conducted, as heterogeneity between studies is anticipated. A modified version of Popay and colleagues (56) framework for developing a narrative synthesis will be used. Synthesis will occur within the three distinct groups outlined in the data extraction section. In the first step, a preliminary synthesis of the outcomes from included studies will be reported. The primary aim of this stage will be to report the proposed psychological processes of psychedelic therapy, the direction of their effect and other relevant design features (e.g. participant demographics, the psychedelic administered) of each included article. Where multiple publications from the same study or dataset exist, these will be narrowed into a single summary. Next, a between study analysis will be undertaken. This will involve an exploration of how proposed processes may overlap with one another, followed by comparing the psychological processes reported by each study, and analysing how they may, or may not, be working together to change depression symptoms. In the final step, the robustness of the synthesis will be assessed. This will involve analysing the quality assessment results produced during the data extraction stage, study designs and the quality of measures used (e.g. method of measuring depression symptoms) to determine if some findings should be weighted more highly than others.

**Discussion**
There are currently no systematic reviews exploring the psychological processes of classic psychedelic therapy in the treatment of depression symptomology. To date, reviews have focused on establishing treatment efficacy, understanding the neurological mechanisms of change, or have been broad in their aims (e.g. including a variety of drug classes or disorders). A review on the psychological processes is needed so current evidence can be collated and gaps in the literature identified. Furthermore, it is important to prompt further research into psychological processes alongside the existing focus on treatment efficacy. Research into other therapies for psychological disorders has heavily focused on establishing treatment efficacy (57). While this is important, the lack of focus on understanding how the intervention may be working has led to poorly understood treatments where the ‘active’ components are unknown. Placing greater importance on researching the underlying processes of treatments may allow for the development of interventions that are maximally efficient and effective (57). The present review aims to address these shortcomings of previous psychological treatment research in the field of psychedelic therapy.

**Limitations**

It is anticipated that the proposed systematic review will have several limitations. Heterogeneity between included studies, such as differences in study design, the psychedelic used, dosage and method of measuring depression symptoms, is expected. This may limit the capability of synthesising study outcomes in a meaningful way. Heterogeneity, as well as the anticipated lack of empirical, quantitative research, has meant a narrative synthesis will be used in conducting this review. Narrative synthesises are at increased risk of being biased by researcher’s opinions, which we intend to minimise through the rigorous methods detailed in this protocol. Finally, we acknowledge that, as this body of research is in its preliminary stages, this review will by no means provide a comprehensive and definitive understanding of the psychological processes occurring in psychedelic therapy for depression. Rather, we aim to present the current state of the literature and generate candidate variables that warrant further investigation.

**Abbreviations**

LSD – Lysergic Acid Diethylamide

DMT - N, N-Dimethyltryptamine

DMN – Default Mode Network

**Declarations**

*Ethics approval and consent to participate*

N/A

*Consent for publication*
Availability of data and materials

Competing Interests

The authors declare that they have no competing interests.

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Author Contributions

LJ conceived and designed the systematic review. GM, MN and PL contributed to the development of the systematic review conception and design. LJ drafted the manuscript. LJ, GM and PL assisted in revising the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Example search strategy in Scopus
TITLE (psychedelic OR hallucinogen OR tryptamine OR phenethylamine OR lsd OR
"Lysergic acid diethylamide" OR psilocybin OR psilocin OR psilocybe OR "magic
mushrooms" OR dmt OR "N,N-DMT" OR “N,N-Dimethyltryptamine” OR
dimethyltryptamine OR ayahuasca OR “Banisteriopsis caapi” OR “Banisteriopsis” OR
“Psychotria viridis” OR hoasca OR mescaline OR peyote OR “San Pedro” OR ceremony*
OR psychotomimetic OR psilocibin OR psilocybine OR “3,4,5-Trimethoxyphenethylamine”
OR trimethoxyphenethylamine AND NOT microdos* AND NOT ketamine AND NOT
dance movement therapy” AND NOT “disease modifying therapy” AND NOT “NPS”
AND NOT salvi*

AND ALL ( depress* OR "mood disorder" OR “affective disorder” OR
“psychopathology” OR “mental illness” OR “mental health” OR “treatment resistant”
OR “major depressive disorder” OR “depress* symptom” OR suicide*
AND ALL ( "psych*proces*" OR mediator OR moderator OR mechanism OR "mecha
nism of change" OR “mechanism of action” OR affect OR avoidance OR acceptance OR
mindful* OR "emotional process*" OR "therapeutic potential" OR “think*” OR
“emotional state” OR decentering OR values OR “psych* flexibil*” or cognit* OR
motivation OR personality OR “personality style” OR avoidance OR wellbeing OR
“quality of life” OR “self-concept” OR “behavio* activat*” OR set OR setting OR
rumination OR perception OR reinforc* OR spirit* OR open* OR “experiential
breakthrough” OR “ego dissolution” OR “ego death”)

