



STUDY PROTOCOL

Clinical Psychedelic Therapy Research Involving Adolescents: Protocol for a Scoping Review of Intervention Studies

[version 1; peer review: 1 approved with reservations]

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Abstract

Background

Recent years have seen renewed clinical interest in the therapeutic potential of classical psychedelics, such as psilocybin, LSD, DMT, and mescaline. While modern studies have focused on adult populations, adolescents under 18 are routinely excluded due to regulatory, legal, and ethical challenges. Although there exists observational data and historical studies from 1959 to 1974 focusing on persons under 18, these earlier trials do not meet contemporary scientific and ethical standards. Hence, despite growing interest in the intersection of adolescent mental health and psychedelic therapy, it is unclear whether any controlled clinical research has been conducted with adolescents in the 21st century. To address this gap, we intend to conduct a scoping review of clinical studies involving psychedelic drug administration, including psychedelic-assisted therapy, in adolescent populations. The present contribution is a protocol for this scoping review.

Methods

Open Peer Review

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1

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 1. Omer Syed, University of Toronto, Toronto, Canada

view

Any reports and responses or comments on the article can be found at the end of the article.

Our scoping review will adhere to the methodological framework of Arksey & O'Malley (2005), which involves five stages: (1) identifying the research question, (2) developing the search strategy, (3) setting inclusion criteria, (4) extracting data, and (5) presenting and analysing the results. We will include both peer-reviewed sources and study protocols that explicitly present evidence of an interventional study involving the administration of psychedelic drugs to adolescents under the age of 18 in the years 2000 - present. We will search for relevant studies in Pubmed (includes MEDLINE), EMBASE, APA PsycInfo, Cochrane Review Library, Web of Science, Cumulated Index to Nursing and Allied Health Literature (CINAHL) and Google Scholar. Clinical trial registers will also be searched, including the USA-based ClinicalTrials.gov and other global registers. Two raters will independently assess articles for eligibility, with disagreements to be resolved by a third reviewer. Data from eligible articles will be charted using a standardized data extraction form. The data will be reported following PRISMA-ScR guidelines.

Plain Language Summary

In recent years, there has been renewed interest in the potential of psychedelic drugs—such as psilocybin, Lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (DMT), and mescaline—for treating mental health conditions. Most modern clinical studies involving these substances have focused on adults, while adolescents under the age of 18 are routinely excluded due to stricter regulations and ethical concerns. Although some controlled research on psychedelic therapy for young people was conducted between 1959 and 1974, those older studies do not meet today's scientific and ethical standards. More recently, a few surveys and case reports have looked at psychedelic use in adolescents, but no controlled clinical studies appear to have been conducted with this group in the 21st century. We aim to conduct a systematic scoping review of the literature to better assess this.

We will include both published and unpublished sources if they explicitly present evidence of a clinical intervention study involving the administration of psychedelic drugs to adolescents under the age of 18 since 2000. We will search for relevant studies in Pubmed (includes MEDLINE), EMBASE, APA PsycInfo, Cochrane Review Library, Web of Science, Cumulated Index to Nursing and Allied Health Literature (CINAHL) and Google Scholar. Clinical trial registers will also be searched, including the USA-based ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Cochrane Central Register of Controlled Trials (CENTRAL) and the UK-based International Standard Randomized Controlled Trial Number ISRCTN Registry. Sources will be excluded if the full text is inaccessible or the main text is in a language other than English. Two reviewers will assess articles for eligibility: one reviewer reviews 100% with a second reviewer reviewing a random selection of 20% of titles and abstracts. Data from eligible articles will be charted using a standardised data extraction form.

Keywords

Psychedelic, adolescent, clinical research, psychedelic-assisted therapy, intervention study, scoping review, protocol

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Introduction

In recent years, there has been a resurgence of clinical research investigating the therapeutic potential of classical psychedelic drugs, such as psilocybin, Lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (DMT) and mescaline. Modern clinical research involving classical psychedelic drugs has primarily focused on adults, and barring adolescents under the age of 18 has become a standardized exclusion criterion for clinical studies. Given the greater regulatory obstacles and legal restrictions placed on paediatric drug trials, as well as heightened ethical concerns about studying psychedelic therapies in adolescent populations, it remains unclear if any recent clinical psychedelic therapy studies have included this population.

From 1959 to 1974, some controlled research into the use of psychedelic drugs, particularly LSD, was conducted for the treatment of paediatric mental illness. However, the scientific and ethical standards of research have drastically changed and improved since this period, and research from this period fails to meet contemporary standards (Edelsohn & Sisti, 2023; Izmi *et al.*, 2024). Major concerns included bias, inconsistent use or invalidity of psychometric measurements, limited therapeutic options, misreporting of neutral or negative findings, and the absence of standardized ethical principles and regulations for drug research involving human subjects (Edelsohn & Sisti, 2023; Sigafos *et al.*, 2007). Thus, we focus on identifying clinical research in the 21st century, which roughly coincides with the so-called “renaissance” in clinical psychedelic research in Western biomedicine (Yaden *et al.*, 2021).

There is some contemporary observational research on the psychological effects of psychedelic use in adolescents drawing on self-reported survey data, as well as case reports. However, recent publications from experts investigating the intersection of adolescent mental health and psychedelic therapy reported finding no instances of controlled clinical research involving psychedelic therapy in adolescent populations since the 1970s (Izmi *et al.*, 2024; Sutherland *et al.*, 2025). We found no published scoping or systematic reviews that investigate these reports. Therefore, a scoping review is appropriate for this topic due to the potentially limited or unknown evidence available. This approach is well-suited to mapping the breadth of

clinical psychedelic use in adolescents, identifying knowledge gaps, and synthesising studies with diverse outcomes and designs (Peters *et al.*, 2020).

Aim: This scoping review aims to identify any clinical intervention studies involving the administration of psychedelic drugs since 2000 to adolescents under the age of 18.

Methods

Stage 1 - Research question

Arksey & O’Malley’s (2005) framework is used to organise this scoping review in five stages, beginning with formulating the research question to guide the review. The main research question for this review is: What is known about the administration of psychedelics to adolescents in regulated clinical settings since the year 2000?

Stage 2 - Search strategy

The PICOS criteria (Richardson *et al.*, 1995) as outlined in Table 1, was used to develop the search strategy (Table 2). Searches will be adapted to each journal, but will include at minimum “adolescents,” “psychedelic,” and “clinical” and filtered to studies published from 2000 to present. This is to ensure all studies investigating the administration of psychedelics to adolescents in regulated clinical settings are identified.

Timeframe

We seek to identify studies from 2000 and onwards. The turn of the 21st century roughly coincided with the “renaissance” of interest in clinical psychedelic therapy research in Western biomedicine after a lengthy period of abolition, with new clinical psychedelic research published as early as 2006 (Yaden *et al.*, 2021). This included the approval of pilot studies for the use of MDMA therapy for chronic treatment-resistant PTSD patients by both the US Food and Drug Administration and Spanish Ministry of Health (Doblin, 2002). By searching from 2000 onwards, we exclude psychedelic research conducted on children with mental illness from the 1950s to 1970s, before the widespread prohibition on psychedelic research in the West. These studies have already been surveyed, discussed, and methodologically and ethically critiqued in the literature (e.g. Edelsohn & Sisti, 2023). Concerns included bias, inconsistent use of psychometric scales, limited therapeutic options,

Table 1. PICO definitions.

Element	Details
Population	Adolescents aged 10 – 17 years enrolled in regulated clinical studies or being treated for mental health concerns, globally.
Intervention	Psychedelic drugs or psychedelic-assisted therapies.
Comparator	Any, including placebos, other treatments, and none.
Outcome	Any outcome measured in a clinical setting, e.g., related to mental health, palliative care, or pain control.
Study Designs	Qualitative and quantitative, interventional studies and expanded access or observational studies tied to an intervention study, in a clinical setting.

Table 2. Core search terms and boolean query.

Concept	Boolean query
Adolescent	adolescen* OR young person OR young people OR youth OR teen* OR juvenile OR minor OR ped/paediatric OR child* OR high school OR middle school OR secondary school OR sixth form
AND	
Psychedelic	Psychedelic OR hallucinogen OR 5-HT2A agonist OR psilocybin OR psilocin OR magic mushrooms OR LSD OR lysergic acid diethylamide OR ayahuasca OR DMT OR dimethyltryptamine OR NN-DMT OR 5-MEO-DMT OR MDMA OR 3,4-methylenedioxyamphetamine OR ecstasy OR molly OR Mescaline OR peyote
AND	
Clinical research	treatment OR intervention* OR clinical trial OR clinical research OR clinical therap* OR Psychedelic-assisted OR psychedelic therap* OR psychotherap*

misinterpretation of neutral or negative findings, and the absence of standardized ethical research principles prior to the Belmont Report (Sigafoos *et al.*, 2007). The scientific and ethical standards of research have drastically changed and improved since this period, and research from this period fails to meet contemporary standards (Edelsohn & Sisti, 2023).

Key terms and their definitions

Adolescent

The term adolescent refers to individuals on the spectrum of development between puberty and adulthood, which can fall within a broad chronological age range of about 10–24 years (Sawyer *et al.*, 2018). However, exclusion criteria in most modern clinical drug research specifically excludes adolescents under the age of 18. This age threshold typically aligns with laws and research ethics guidelines that regulate the rights, protections, and agency of legal minors. As the aim of this review is to identify whether any clinical research has been conducted within this typically excluded group, we define adolescents as legal minors under 18 (i.e., excluding age 18 and up), which matches with the definition employed in standardized research exclusion criteria. Studies that include a wider age span of adolescents (e.g., 16 – 24 years), will be included and we will report data related to participants age 10 – 17 years where possible.

Psychedelic

Understood as a pharmacological category, *classical psychedelic* typically refers to a drug that falls within three classes: tryptamines, phenethylamines, and lysergamides (Lowe *et al.*, 2022). For this scoping review, we define psychedelics as any

psychoactive substance belonging to one of these classes, provided its pharmacological mechanism of action primarily involves serotonergic pathways or activation of the 5-HT2A receptor (Nichols, 2016). This criterion excludes certain phenethylamines, such as amphetamines, which function as stimulants rather than psychedelics and do not primarily act through serotonergic pathways (Martin & Le, 2023; Sitte, 2023).

According to this definition we include psilocybin, LSD, mescaline, NN-DMT and 5-MeO-DMT. Some of these (e.g., psilocybin mushrooms, peyote mescaline) are found in nature and have been used in certain Indigenous communities for ceremonial and communal purposes within the context of particular belief systems and traditions of use. Others (e.g., LSD, synthetic psilocybin) were developed by scientists within the past century and may have different associations within Western culture (Jacobs *et al.*, 2024).

A broader set of drugs may alter consciousness and share psychopharmacological and neurophenomenological similarities with classical psychedelics. Among these broader examples are MDMA, ibogaine, ketamine, salvia, scopolamine, and cannabis. From this subset, we include only MDMA. Although MDMA may not meet strict pharmacological criteria for classical psychedelics, MDMA causes a release of serotonin, dopamine, and norepinephrine to elicit its effects (Check, 2004; McCann *et al.*, 1994; Nichols, 1986), and can also interact with the (5-HT)2A receptor. Furthermore, MDMA is predominantly used in clinical medicine within the specific context of drug-assisted psychotherapy, similar to psychedelics. We thus believe the inclusion of MDMA is important for

comprehensive reviews in the context of clinical psychedelic therapy.

We exclude all other non-classical psychedelics from our definition as they vary widely in their drug classes, mechanisms of action, sociocultural and medical contexts of use, and acute subjective effects. For some of these drugs such as ketamine, their use within clinical medical research varies significantly and often involves biomedical use (e.g., anesthesia) outside the framework of psychedelic therapy for mental illness.

Clinical Research

We define clinical research as studies conducted in a regulated clinical biomedical context, including interventional studies, observational studies (cross-sectional, prospective and retrospective cohort studies and case-control studies), and expanded access studies. These can be both peer-reviewed and grey literature, however, to be included must describe the administration of a psychedelic in a clinical research setting.

Database selection

We searched for other broad systematic and scoping reviews related to psychedelic research, and compiled a cumulative list of clinical research databases from three review protocols detailed in Table 3. We then added a list of clinical trial databases which may include studies that are not yet completed or published. We also added some broad research databases including Google Scholar which were not included in the cited systematic reviews, but which reinforce the comprehensiveness of our review.

Based on the these reviews and initial conversations with Library Services at Imperial College London, the following databases will be searched for this review: Pubmed (includes MEDLINE), EMBASE, APA PsycInfo, Cochrane Review

Library, Web of Science, Cumulated Index to Nursing and Allied Health Literature (CINAHL) and Google Scholar. Clinical trial registers will also be searched, including the USA-based ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Cochrane Central Register of Controlled Trials (CENTRAL) and the UK-based International Standard Randomized Controlled Trial Number ISRCTN Registry.

To identify additional studies, the reference lists of related reviews and included studies will be hand searched and experts in the use of psychedelics in clinical settings will be consulted.

Stage 3 - Study selection

If enough potential articles are found (e.g., >5,000), search results will be imported into EPPI-Reviewer 6 software, otherwise the titles and abstracts will be screened in Covidence. Eppli-Reviewer is an online software developed by the EPPI Centre (Thomas *et al.*, 2023) which uses machine learning to screen titles and abstracts for eligibility based on the inclusion and exclusion criteria outlined in Table 4. After removing duplicates, the machine learning model will be trained on the initial screening of 1000 titles and abstracts (Zantvoort *et al.*, 2024) by two reviewers with approximately an 80/20% split (one reviewer reviews 100% with a second reviewer independently reviewing a randomly selected 20% of titles and abstracts). A classifier model will be created based on these screening decisions which will grade the remaining unscreened studies and mark a threshold for irrelevant studies (Thomas *et al.*, 2023).

Full-texts of the included titles/abstracts will then be imported into Covidence online software (Veritas Health Innovation, Melbourne, Victoria, Australia) for review. Two authors will review full-texts independently for eligibility. Disagreements will

Table 3. Database selection based on similar reviews.

First author, year	Title	Database searched
Hermann <i>et al.</i> , 2023	Scoping Review of Experiential Measures from Psychedelic Research and Clinical Trials	PubMed Embase Scopus APA PsycInfo
Ko <i>et al.</i> , 2023	Psychedelic therapy for depressive symptoms: A systematic review and meta-analysis	Embase MEDLINE PsychINFO Cochrane Central Register of Controlled Trials
Ko <i>et al.</i> , 2022	Psychedelics, Mystical Experience, and Therapeutic Efficacy: A Systematic Review	Embase MEDLINE APA PsycInfo

Table 4. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Population	Adolescents aged 10 – 17 years old	Children under 10, adolescents Adults aged 18 years and over
Intervention (Investigative substance)	5-HT _{2A} receptor agonists (e.g., psilocybin, LSD, mescaline, peyote, NN-DMT and 5-MeO-DMT) MDMA (3,4-methylenedioxymethamphetamine)	Ketamine Ibogaine Ketamine Salvia Scopolamine Cannabis
Outcome (Indication for use)	Any, (e.g., mental health, palliative care, pain control)	N/A
Comparator	Any active or inactive substance or no comparator	N/A
Study status	Completed Ongoing Recruiting Not yet recruiting	N/A
Study design	Interventional studies: Randomised control, uncontrolled, and non-randomised trials Observational studies: cohort, cross-sectional, case-control, only if related to an interventional study	Observational studies not related to an interventional study
Publication types	Peer-reviewed publications Non peer-reviewed: Clinical trial registrations Study protocols Statistical analysis plans Reports Working papers Conference abstracts Pre-prints	Case report or case series Animal models Reviews Opinion pieces Theses
Study setting	Clinical settings including expanded access	Observational studies of psychedelic drug use in recreational, naturalistic, and non-clinical contexts
Location	All countries	N/A
Timeframe of published studies	Published 2000 to present	Published before 2000
Language	English	All other languages

be discussed to reach consensus, with a third author weighing in if needed. For studies reporting on data of the same cohort, the newest study or one with the largest sample size will be included. The number of studies screened at each stage, and the reasons for exclusions will be reported using a PRISMA flow diagram (Tricco *et al.*, 2018).

Stage 4 - Data extraction

Two reviewers will independently extract data for included studies that will be checked independently by a third reviewer. A data extraction template was developed (see Table 5), based on adapted versions of the CONSORT 2010 checklist for randomised trials (Schulz *et al.*, 2010), and STROBE checklists

Table 5. Data extraction template.

Field	Description	Options
Study ID	Lead author last name and year study registered on clinical trial registry or year published	
Title	Study title	
year registered	Year study registered or published	
url	website or DOI	
country	Country the study takes place and participants will derive from	
publication_type	Type of publication (Can select multiple options)	peer-reviewed journal article non-peer-reviewed: clinical trial registry non-peer-reviewed: study protocol non-peer-reviewed: statistical analysis plan non-peer-reviewed: report non-peer-reviewed: working paper non-peer-reviewed: conference abstract non-peer-reviewed: pre-print Other (describe)
study_status	Study status, as reported (Can select multiple options)	completed ongoing recruiting not yet recruiting study protocol Other (describe)
phase	Clinical trial phase	
aim	Aim of the study	
main_study_design	Main intervention study design (Can select multiple options)	intervention: randomised control trial (RCT) intervention: uncontrolled clinical trial intervention: non-randomised clinical trial intervention: unknown/unclear/not described Other (describe)
secondary_study_design	Secondary observational study design (Can select multiple options)	observational: cohort, retrospective observational: cohort, prospective observational: cross-sectional observational: case-control observational: unknown/unclear/not described Other (describe)
fu_duration	Follow-up duration	
blinding	Type of masking and who masked	e.g., Triple (Participant, Investigator, Outcomes Assessor)
n_target	Target sample size	
condition	Medical condition being treated	
population	Target population	

Field	Description	Options
inclusion_age	Inclusion age range	
inclusion_sex	Inclusion sex	
inclusion_criteria	All inclusion criteria	
exclusion_criteria	All exclusion criteria	
psychedelic	Psychedelic investigated	
intervention(s)	Intervention(s) being assessed	
comparator(s)	Comparator(s) to the intervention(s)	
primary_outcome(s)	Primary outcome(s)	
Results		
n_total	Total sample size	
main_finding(s)	Main findings	
funding	Funder(s)	
ethics	Ethical review details	
coi	Reported conflicts of interest	

(von Elm *et al.*, 2007) for observational studies. The tool will be piloted on exemplar articles of interventional and observational studies. Extracted data will include at minimum: lead author's last name, publication year, article title, country, study design, sample characteristics, psychedelic drug/therapy details and main findings.

Stage 5 - Summarising and reporting outcomes

The results of the scoping review will be summarized in a table cataloging key study characteristics including: population, psychedelic drug used, target mental health condition, and study type. We will present the findings according to PRISMA for Scoping Reviews (PRISMA-ScR) guidelines (Tricco *et al.*, 2018). The results will also be formulated into a plain language summary. This plain language summary will be formulated specifically for forthcoming manuscripts on the topic of adolescent inclusion in future clinical psychedelic therapy research.

Conclusion

Adolescents under the age of 18 are routinely excluded from clinical psychedelic research due to regulations and ethical concerns, and it remains unclear whether any controlled clinical research has been conducted in this population in the 21st century.

This scoping review will help shed light on the extent of modern clinical psychedelic research in populations under 18, and serve as an important foundation for interdisciplinary dialogues about if and how to proceed with future research in this population group.

Understanding this research landscape is essential for informed ethical dialogue, and research ethics decision-making, and responsible policy development in the context of clinical psychedelic therapy research in youth populations.

Ethics and consent

Ethical approval and consent are not required to perform this review.

Data availability

No data are associated with this article.

Software availability

Publish or Perish - will be used to export Google Scholar search results into a format that can be uploaded into Eppi-Reviewer and Covidence. This software is available free for use.

Zotero - References from database searches will be uploaded here as needed to export the references into a format able to be uploaded to Eppi-Reviewer and Covidence. Final references for included studies will be managed using this software. This downloadable software is available free for use.

Eppi-Reviewer6 - Titles and abstracts will be uploaded to this online software and aid in screening them for eligibility. A free trial version is available.

Covidence - Full-text articles will be uploaded here for screening. Data from eligible articles will be extracted using a standardised template the authors will develop using this online software. This online software is available as a paid yearly or organizational subscription.

Acknowledgements

Patient consent for publication is not required given our methodology. External ethics review is not necessary given this project's analysis of pre-existing data. No patient or public involvement was necessary to design this scoping review protocol, nor will it be required for subsequent data analysis. In response to growing sociopolitical interest in psychedelics, we intend to present our research to academics, clinicians, and politicians at relevant conferences and symposia, in addition to publishing our findings.

As suggested by Porsdam Mann *et al.* (2024), we note the following regarding our use of large language models: "Any use of generative AI in this manuscript adheres to ethical guidelines for use and acknowledgment of generative AI in academic research. Each author has made a substantial contribution to the work, which has been thoroughly vetted for accuracy, and assumes responsibility for the integrity of their contributions." Specifically, ChatGPT 4o was used to check spelling, grammar, improve word choices, and draft the plain language summary.

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Omer Syed 

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This article is a study protocol for a scoping review of adolescents receiving psychedelic therapy. The area of inquiry is topical and the subsequent review can synthesize the literature on adolescent populations receiving psychedelics. The manuscript is well written and there are no major methodological concerns, but addressing the comments below can improve the article.

Introduction

1. The introduction section states that there are no scoping or systematic reviews on the topic of adolescents and psychedelic therapy, which serves as a rationale for conducting this scoping review. I recommend mentioning a few empirical studies on the topic that the authors may be aware of prior to conducting the systematic search. This will help set the stage for the results of a comprehensive search.
2. Provide a citation for this claim "There is some contemporary observational research on the psychological effects of psychedelic use in adolescents drawing on self-reported survey data, as well as case reports."
3. The introduction section is quite brief, and can benefit from being further expanded. Specifically, there is not a sufficient extent of rationale provided for the need to examine adolescents receiving psychedelic therapy aside from the fact that it has not been published on before. Perhaps factors such as epidemiological data reflecting increased recreational psychedelic use among adolescents, potential differences in psychedelic-induced neuroplasticity based on age, or increasing mental health disorders amongst the youth makes this an especially interesting area of inquiry.

Methods

1. Database selection Table 3: Since there are numerous scoping reviews on the use of psychedelics, what criteria guided the selection of the 3 reviews presented in Table 3? Please mention in text.
2. "Two reviewers will independently extract data for included studies that will be checked independently by a third reviewer". If possible and already agreed upon, please specify the authors responsible for these tasks by their initials.

3. Table 4: Ketamine is listed twice in the Intervention's Exclusion criteria column.
4. Table 4: Since the review will include non-peer reviewed studies such as study protocols, working papers, and conference abstracts, please justify the exclusion of case reports and case series. Case reports (especially peer-reviewed) can be of value in an under-explored research area such as this.

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Naturalistic and clinical use of psychedelics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
