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THÈSE

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par

Lisa BOUCHET

le 13 octobre 2022

Prévalence des personnes âgées dans la recherche clinique sur les thérapies assistées par les psychédéliques : Une revue systématique de la littérature

Directeurs de thèse : Pr Antoine YRONDI et Dr Yvan BEAUSSANT

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AUTEUR : Lisa BOUCHET
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Avant-propos. La littérature scientifique actuelle suggère une efficacité des thérapies assistées par les psychédéliques dans plusieurs indications psychiatriques. Elle concerne majoritairement une population jeune. L'efficacité et la tolérance chez la personne âgée dans le cadre d'études contrôlées restent largement inconnues.
Objectif. Déterminer la prévalence des personnes âgées inscrites dans les essais cliniques sur les psychédéliques et explorer les données de sécurité dans cette population.
Méthode. Nous avons entrepris une revue systématique de la littérature en respectant les recommandations PRISMA 2020. Nous avons inclus toutes les études cliniques, publiées en anglais ou en français, utilisant des substances psychédéliques (psilocybine, DMT, LSD, MDMA, ayahuasca and ibogaïne) pour traiter des troubles psychiatriques. La recherche a été réalisée sur les bases de données MEDLINE, PSYCHINFO et EMBASE.
Résultats. 4235 abstracts ont été évalués, dont 501 articles complets, l'inclusion finale contient 32 articles. Sur les 1103 patients inclus, au moins 17 ont plus de 65 ans, soit une prévalence d'environ 1.5 %. Aucun effet indésirable grave associé aux psychédéliques n'a été rapporté dans cette population.
Conclusion. À ce jour, les personnes âgées ont largement été exclues de la recherche clinique sur les thérapies assistées par les psychédéliques. De nouveaux travaux évaluant la tolérance et l'efficacité de ces thérapies dans cette population présentant des spécificités liées à l'âge et des comorbidités fréquentes semblent nécessaires.

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Title: Prevalence of Older Adults in Psychedelic-Assisted Therapy trials: A Systematic Review

Key Message: This study presents a synthesis of the scientific evidence on the prevalence of older adults in psychedelic assisted therapies in its indication in palliative care (existential suffering in cancer patients), in psychiatry (MDD, PTSD) and addictology. We focused on the existing data about the tolerability of psychedelic therapies for elderly people.

Mots-Clés: Psychedelic, Psilocybin, LSD, MDMA, Ayahuasca, DMT, Older Adults, Elderly, Palliative Care, Psychiatry, Demoralization, Existential Distress, PTSD, MDD, Anxiety

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Discipline administrative : PSYCHIATRIE

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Faculté de médecine Toulouse-Purpan – 37 Allées Jules Guesde – 31000 Toulouse – France

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Serment d'Hippocrate

«Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leur raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime
si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.»

Remerciements

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A Antoine,

Enfin, je souhaite écrire aujourd'hui tout l'amour que je te porte.
Du Goutarou au Pic du Midi d'Ossau, j'espère pouvoir toujours marcher vers un ciel étoilé avec toi. A nos aventures passées et futures !

A François Tosquelles (1912-1994),
Dont l'héritage inspire ma pratique quotidienne.

Table des matières

Liste des abréviations

AEs: Adverse events

BPD: Borderline Personality Disorder

DPT: Dipropyltryptamine

DMT: Diméthyltryptamine

FDA: Food and Drug Administration

LSD: Diéthyllysergamide

MDMA: 3,4-méthylènedioxyméthamphétamine

MDD: Major Depressive Disorder

PTSD: Post-Traumatic Stress Disorder

SAEs: Serious adverse events

SD: Standard Deviation

WHO: World Health Organization

Abstract

Background.

Growing clinical interest in psychedelic-assisted therapies has led to a second wave of research involving psilocybin, LSD, ayahuasca, MDMA and other substances. Data suggest significant potential to address mental health conditions that are particularly prevalent in older adults such as depression, anxiety, existential distress and Post-Traumatic Stress Disorder. However, most of existing clinical research involved younger individuals and the safety and efficacy of psychedelic use in older adults in controlled research settings remain largely unknown.

Objective.

To determine the prevalence of older adults enrolled in psychedelic clinical trials and explore safety data in this population.

Method.

We undertook a systematic review of existing psychedelic research following the 2020 PRISMA guidelines. We included all trials, published in English or French, using psychedelic substances (psilocybin, DMT, LSD, MDMA, ayahuasca, and ibogaine) to treat psychiatric conditions and/or serious illness-related distress. We excluded studies on healthy individuals. A literature search using MEDLINE, PSYCHINFO and EMBASE was performed.

Results.

We reviewed 4215 abstracts obtained from the data bases query, of which 501 qualified for further review of full text papers. Twenty additional full texts were identified through other sources and analyzed. We found 55 studies meeting our eligibility criteria, including 23 secondary analyses. Over the 1103 individuals included in the different studies, at least 17 were above 65-year-old, with a prevalence of approximately 1.5%. No psychedelic-related serious adverse events (SAEs) were reported in clinical trial that included older adults. We describe in details AEs that occurred in 10 older adults included in recent psilocybin studies.

Conclusion.

To date, older adults have been largely excluded from clinical trials assessing the safety and efficacy of psychedelic-assisted therapies. Given the clinical needs in this population, as well as safety issues due to frequent comorbidities, clinical trials focusing on the safety and efficacy of psychedelic-assisted therapies to improve mental health conditions and well-being in older adults are warranted.

Background

The word *psychedelics* was invented in 1956 by the writer Aldous Huxley and the psychiatrist Humphry Osmond. (1) Psychedelic combines the words psychē (ψυχή, 'soul') and dēloun (δηλοῦν, 'to make visible, to reveal'). (2)

Historically, different substances (known today as classic serotoninergic psychedelics) have been used in different traditional groups: mescaline, which is the active principle of peyote cactus, used by indigenous North Americans, psilocybin by Aztec shaman and ayahuasca, a decoction of a liana *Banisteriopsis caapii* and perennial *Psychotria viridis* used traditionally by natives of the Amazon Valley of South America. They were all used during spiritual and healing ceremonies. (3)

In 1943, Alfred Hofmann discovered LSD psychoactive effect. This discovery was followed by a large and global interest for psychedelics by psychiatrists in Europe and North America for almost three decades. (2) Between 1950 and 1970, more than 1000 clinical studies were published using psychedelics as a treatment for psychiatric conditions and have been tested on around 40 000 individuals. (4) Clinical research was curbed when the Controlled Substances Act of 1970 was approved, LSD and other psychedelics known at the time were placed into the most restrictive category of drugs, Schedule 1. (3)

Finally, interest has grown around psychedelic assisted psychotherapy for two decades, especially since the Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation to MDMA for the treatment of posttraumatic stress disorder PTSD in 2017; and psilocybin to treat major depressive disorder (MDD) in 2018 and 2019.

Nowadays, moral suffering is still a main issue in psychiatry, addictology and in palliative care.

While depression is the main burden disease worldwide by years of lost by disability (YLD) (5), cancer is one the leading cause of death with more 18 millions of death in 2020 (6). Existential distress in cancer patients, depressive disorder, addictions and post-traumatic stress disorder are main issues for clinicians in their daily practice.

Elderly patients have more risk than younger patients to declare a medical condition. For depression, we estimate that the 3,8 % of the population suffers from depressive disorder, it raise to 5,7 % for elderly patients above 60 years-old. (7) Unfortunately, older adults are underrepresented in clinical research. (8)

Actual therapeutics presents partial efficacy and a poor tolerability in psychiatry; many patients stop their medication by themselves due to adverse effects or poor efficacy. (9)

This last decades, a regain of clinical research in psychedelics therapy arose and new clinical data are very promising. Clinical data are still lacking, especially concerning elderly patients. We have done a PubMed research in April 2022 (“psychedelic” AND ”elderly”[Title/Abstract]), we found only 3 results: two case study (10,11) and a non-systematic narrative review (12).

In the present study, we aim to evaluate the prevalence of elderly patient (i.e., 65 years old and above) in psychedelics assisted therapies, describe its use and tolerability in its indication in psychiatry, addictology and in palliative care for older adults.

Methods

Eligibility criteria

Types of studies. This systematic review included publications reporting clinical studies with an objective and validated outcome measure (randomized or not, with a control group or not) published in peer-reviewed journals from inception of data base until 1st of January 2022. Observational and retrospective studies, commentaries, opinions, letters or editorials were excluded. We excluded articles without objective outcome measures nor validated rating scale. Only articles in English or French language were included. There were no limitations regarding year of publication.

Types of participants. Healthy participants were excluded from our study. We included patients diagnosed with serious illness, psychiatric diagnosis, addictology issues or suffering from neurosis. There were no limitations regarding age, gender or ethnic origin. We focused on data available for participants over 65 y.o.

Types of interventions/exposure. All interventions based on the use of psilocybin, DMT, LSD, MDMA, ayahuasca, and ibogaine were included, with or without a component psychotherapy. Articles reporting the use of cannabis, ketamine or non-serotoninergic substances were excluded. We excluded the use psychedelic substance to treat psychosis or for model of psychosis.

All type of non-pharmacological interventions in adjunct with psychedelic-assisted therapy were included and are detailed in this research.

Types of outcomes. We aimed to evaluate the safety and tolerability of psychedelic assisted therapies in elderly patients, we examined all serious and other adverse events and classified them by system (e.g. digestive, neurologic etc.). Nevertheless, we looked at all efficacy and safety outcomes used in the selected studies.

Search strategy

The protocol of this review was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols of 2020 (PRISMA-P).

Preliminary research for keywords was done on the different database. Boolean link words were used in the search algorithm.

The search strategy used was adapted to the specific needs of each database to be consulted for this review: PUBMED, MEDLINE and Google Scholar (*CINAHL/EBSCO, EMBASE, PsycInfo, Web of Science*). The first data extraction was made in April 2019 and an update was done on the 1st of January 2022.

Study records

Data management. The results retrieved from the databases were exported to EndNote or Zotero, duplicate articles were removed. The first selection process was done on EndNote, the second selection process was done on Zotero for convenience of reviewers. We reviewed the bibliography of the articles included to search manually for other sources.

Selection process. The selection of studies was performed by evaluating the titles and abstracts according to the eligibility criteria. Relevant articles were read in their entirety, and those that failed to meet the predetermined criteria for this review were excluded. The first study identification process was carried out independently by two reviewers (YB et ZS) using Rayyan software. The second study identification process was done by LB. In case on inconsistencies, these were discussed and agreed upon, and when necessary, another reviewer was involved so that an agreement could be reached. The reviewers were not blinded regarding the publishing journals, authors, or institutions during any stage of the selection process.

Data Collection Process. The data extraction was carried out manually by LB and covered: authorship, year of publication, study design, description of population (age, gender, comorbidities), psychedelic substance studied (route, posology), medical indication, placebo condition, adjunctive psychotherapy (type, number and duration of sessions), adverse effects related to psychedelic-assisted therapies and main results about symptoms control.

All the authors have reviewed and discussed the content of the table before starting the data extraction.

Data Synthesis and Analysis. We have synthesized the information collected based on the variables of interest for this review through a narrative synthesis approach.

Results were reported in a pragmatic and descriptive manner with textual data from included studies.

Results

Study Selection

A total of 4 215 articles were published record were identified through the initial query on PUBMED, MEDLINE and EMBASE and 20 articles were included manually going through the bibliography of the articles screened. We included a total of 32 studies in our systematic review (13–30,30–43).

A flow chart of identification, screening, review, and selection of studies is presented in Figure 1.

Study characteristics

We included articles from 1967 until 2021. We were not able to include older studies because the methodology wasn't fitting with the actual standards: no standardized diagnostic techniques and no definition of an objective outcome measure.

We found no article written in French language meeting our inclusion criteria.

Concerning the study design, 18 were randomized controlled trials and 14 open-label studies. The randomized studies were mainly done during the last decade and reflect the growing interest around psychedelic-assisted therapies.

We included articles studying classic psychedelics as psilocybin, DPT, LSD, ayahuasca, and non-classical as MDMA. We found 10 studies using psilocybin (13,14,16,17,19,21,22,25,33,38), 9 articles using MDMA (15,18,29–32,34,43,44), 7 using LSD (20,26–28,36,39,42), 3 for ayahuasca (35,37,41) and 2 for DPT (24,40). One study used both LSD and then DPT (23). During the study, one third of the patients received DPT instead of LSD. The research team justified it as a new psychedelic substance with "shorter-acting compound and similar effects" that seems a better alternative for "severely debilitated terminal patients" and it's also an "unknown in nonmedical circles and as yet uncontaminated by adverse lay publicity". (23)

No article using DMT met our inclusion criteria. We found only one article about mescaline or ibogaine, nor they met our inclusion criteria.

The main medical indications were:

- 11 studies about demoralization (disempowerment, sense of helplessness, hopelessness, futility), anxiety or existential distress related to a life-threatening disease (cancer, HIV). They mainly used psilocybin (4 studies) and LSD (5 studies) but also DPT and MDMA (1 study for each).
- 7 studies about chronic and severe PTSD using MDMA.
- 6 studies about resistant or recurrent mild to severe MDD. They used both psilocybin and ayahuasca, 3 studies for each of the molecule.
- Concerning indication in addictology,
    - 3 studies concerning alcohol dependance using respectively psilocybin, DPT and LSD.
    - 1 study about tobacco addiction using psilocybin
    - 1 study for narcotic addiction using LSD
- Finally, there was 1 study concerning psychoneurotic diagnosis (depressive symptoms and anxiety) using LSD, 1 study for Social Anxiety Disorder (SAD) in an autistic population using MDMA and 1 about obsessive compulsive disorder using psilocybin.

Finally, we chose to describe the different types of non-pharmacological interventions like the chosen type of psychotherapy or *set and setting*.

Psychedelic-assisted therapy refers to the administration of psychedelic substance associated with several psychotherapeutic sessions. It has been influenced by the "psychedelic psychotherapy" in the 70's literature with preparatory psychotherapy sessions to establish a good therapeutic alliance, review the patient's life history and give information about the safety and efficacy goals of the drug; closely monitored medication dosing sessions with therapist and/or co-therapist present throughout the drug sessions; and post-dosing integrative psychotherapy during the following weeks. (38)

Researchers used mainly supportive and non-directive psychotherapy in 22 studies. Few other types of psychotherapy have been use like Cognitive Behavioral Therapy (CBT) (25) and Cognitive Behavioral Conjoint Therapy (CBCT) (32), Motivational Enhancement Therapy (MET) for alcohol dependance (14), Dialectal Behavior Therapy (DBT) (19) and finally, Guided Affective Imagery in another study (40).

Four studies didn't have adjunct psychotherapy and for one other study the type of psychotherapy was undisclosed.

The use of set and setting was described in most of the studies, especially those conducted in the last two decades. We describe below the notions of *set and setting* in more details.

We described the main data of the included studies in Table 1 and we detailed the scales used to evaluate primary, secondary outcomes and altered states of consciousness in Table 2.

Prevalence and use of older individuals

Over the 1103 individuals included in the different studies, at least 17 were above 65 y.o. The prevalence of patients above 65 included in the clinical studies of psychedelic assisted therapies was approximately 1.5 %.

In some studies, we were able to collect that the oldest patient was more than 65 y.o. during the study but we had no information about the fact that some other patient's age could be ranging from 50 to 65 y.o..

Safety of psychedelic assisted therapies in elderly patients

We tried to contact the different research teams to ask about the safety data of these specific patients. Some of them answered to our solicitation, you will find the description of the clinical data for each elderly patient in Table 3.

Discussion

Strengths and Limitations

To our knowledge, this study is the first systematic review about older adults in psychedelic-assisted therapies. The main strengths are a global overview of the actual literature in psychedelic-assisted therapy focusing in elderly patients in recent and older literature and the methodology of our study is fitting the actual standards for systematic reviews.

The main limitations are the lack of clinical data for elderly patients in papers studying psychedelic-assisted therapy, the fact that our algorithm couldn't highlight some studies that we included manually, and we may not have had access to a certain number of articles which would meet our inclusion criteria.

Actual concerns about psychedelic-assisted therapy in older adults

We tried to better understand the low rate of inclusion for elderly patients. Stigma in clinical research appeared to be the first reason. Often, they are excluded of clinical research because of comorbidities and the main consequence is the delay for them to access to new drugs. Researchers can also exclude older patients by setting a low age of inclusion before the evaluation of their eligibility for the study.

According to the WHO, between 2015 and 2050, the proportion of the world's population over 60 will jump from 12% to 22% and nowadays approximately 15% of adults aged 60 and over suffer from a mental disorder. (45) We also know that different conditions associated with ageing as renal, cardiac dysfunction can influence pharmacokinetics and pharmacodynamics. Different drug's interactions due to polypharmacy, especially psychotropic drug, can have implication in cognitive impairment, dementia, cardiac, renal, or digestive function.

We need to better understand all these parameters specific to elderly patients when interacting with psychedelic substances.

A study is currently testing the efficacity of psilocybin in depression for patients with mild cognitive impairment or early Alzheimer's disease in John Hopkin's University. The age for inclusion is up to 85 years old and we hope that this early phase 1 study will offer more data on psilocybin's tolerability for elderly. (46)

In one hand, elderly can be more vulnerable to adverse events, but on the other hand, it could have benefic outcomes on a difficult clinical situation as quality of life in neurodegenerative diseases. Could it even help us to reach the challenge of successful aging?

General safety and tolerability

Regarding safety issues, we were, unfortunately, not able to conclude on the elderly population. We chose to detail here data on two serious adverse events (SAEs) possibly related or related to the drug in the 32 studies included. One brief psychotic episode in Grof's study using DPT for alcohol dependance, which responded positively to readmission and antipsychotic treatment (*mellaril*). (24) The authors specified that the patient had severe neurotic syndromes and other stress factors before drug sessions and throughout the study. One other serious adverse event possibly related to the drug is acute increase in premature ventricular contractions in the clinical trial of Mithoefer in 2018 using MDMA to treat resistant PTSD. (44) The patient had exhibited a premature ventricular contraction at baseline. This last participant had an overnight hospital stay for observation and cardiac assessment and recovered fully without evidence for vascular or structural cardiac disease.

Finally, three serious adverse events occurred in the placebo group of Mitchell's study in 2021 with suicidal behaviors (1 patient) and suicidal ideation that led to self-hospitalization. As this serious adverse event happened in the placebo group, we can easily conclude that they were not related to the drug (MDMA).

Political limitation of scientific research on this field

In a second time, we would like to focus on the fact that we found no article written in French language meeting our inclusion criteria. The medical use of classic psychedelics hasn't been approved yet in France. Most clinical trials are achieved in the United State of America. Some European countries allows clinical research on psychedelics assisted therapies : two studies the United Kingdom (16,17), two studies in Switzerland (20,34) and one study in Spain (15).

Bouso et al.'s study in Spain, published in 2008 was closed before the inclusion could be completed (6 patients over 29 patients planned) because of political pressure. They were studying low doses MDMA-assisted psychotherapy for women victims of rape and/or domestic violence suffering from chronic PTSD.

All the clinical studies for the use of ayahuasca that we included were done in Brazil.

Specific and at-risk populations

As most clinical study, the population studied is quite homogenous with educated, socially included individuals and without psychiatric nor somatic comorbidity. Nevertheless, we found two very interesting studies, focusing on at risk population with psychiatric comorbidities. The Savage study in 1973 using LSD for narcotic dependance in an inmate population and 9 (25%) of the 36 subjects in the treatment group maintained total abstinence from narcotics drugs for at least one year opposed to two subjects (5%) of the 37 in the control group ($p<0.05$). The Anderson study in 2020 using psilocybin for the treatment of moderate to severe demoralization for seropositive gay-identified, cisgender men ≥ 50 years old with self-report of HIV diagnosis prior to the clinical availability of protease inhibitors, population that endured a traumatic personal history, various somatic and psychiatric comorbidities. This article is the first known description of adverse effects in patients meeting SCID-5-PD criteria for borderline personality disorder (n=3): severe anxiety and severe high blood pressure during the session (n=2); severe anxiety 10 days after the session and relapse in methamphetamine use (n=1). Further investigations are necessary in patients with a BPD diagnosis.

Set and setting

Finally, we would like to focus on the importance of set (i.e., psychological state of a person) and setting (i.e., a person's environmental context) in psychedelic-assisted therapies. The occurrence of a mystical or peak experience is highly dependent of this two internal and external parameters. (3) We know that the Peak Experience is one of the main determinants for efficacy during drug sessions. (40) Strickland and al. 2021 focused on the musical atmosphere during the drug sessions, where western classical music is usually used, with only empiric knowledge, compared to overtone-based music. The overtone-based music playlist was correlate with higher mystical experiences scores and a slight benefit on biologically confirmed smoking abstinence (66.7% versus 50%) on this small sample of participants (n=10).

Taking care of family carers

As an opening for the future of psychedelic assisted therapies, we found that it can be used not only for patients but also for family carers as it is shown in the Monson study where both patients suffering from PTSD and partners (n = 6 couples) took benefits from MDMA sessions. The results are showing a significant and sustained improvements in clinician-assessed PTSD ($B = -4.64$, $p < .001$), with $d = 1.88–2.25$ at posttreatment and follow-ups and significant improvements in overall patient and partner relationship satisfaction score ($B = 4.55$, $p < .05$, $d = .82–1.22$ for patients and $B = 5.73$, $p < .05$, $d = .64$-$.80$ for partners).

This indication needs further investigations, but it could be a new opportunity for the help of family carers in palliative care and psychiatry.

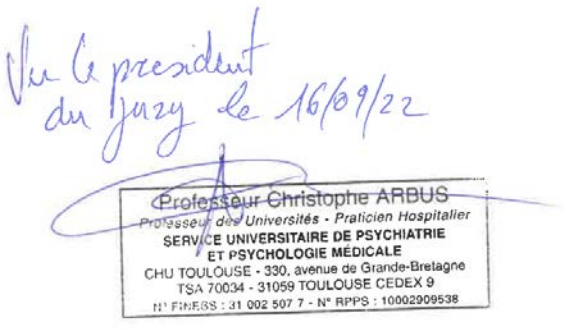
As a final opening, we would like to focus on the procedure of psilocybin-assisted group therapy in Anderson 2020. It's the first study to our knowledge to focus on group psychotherapy which can be cost saving but also emphasize the connection and feeling trust between patients, when a relation of trust with the therapist can be longer to build.

Conclusion

To our knowledge, this study is the first systematic review about older adults in psychedelic-assisted therapies. We demonstrate that patients over 65 accounted for approximatively 1.5% of those included in clinical studies to this day. As no description of the safety and efficacy of this population has been done in the existing articles, the actual knowledge is insufficient to be able to conclude for this specific population.

A global interest is growing around psychedelic assisted therapy. A French independent journalist based in New York, Stéphanie Chayet wrote a book *Phantastica* about her own experience with psychedelics while going through a breast cancer (47), this last year two main articles were published in The New York Times, including one focusing on the use of ayahuasca for senior citizens (48,49). Curiosity around psychedelics has crossed the Atlantic Ocean. This last summer, articles were written in influential French journals like Courrier International after the main publication in JAMA Psychiatry at the end of August of a Phase III study using psilocybin for the treatment of alcoholic addiction, or Le Monde which dedicated a series of 6 articles to psilocybin.

Regarding the growing interest in the scientific and mainstream literature, we hope our work will challenge researchers to focus on this important question by enlarging their age for inclusion and to be more willing to include older patients in clinical studies.



Supplementary materials

Fig. 1. Article identification process

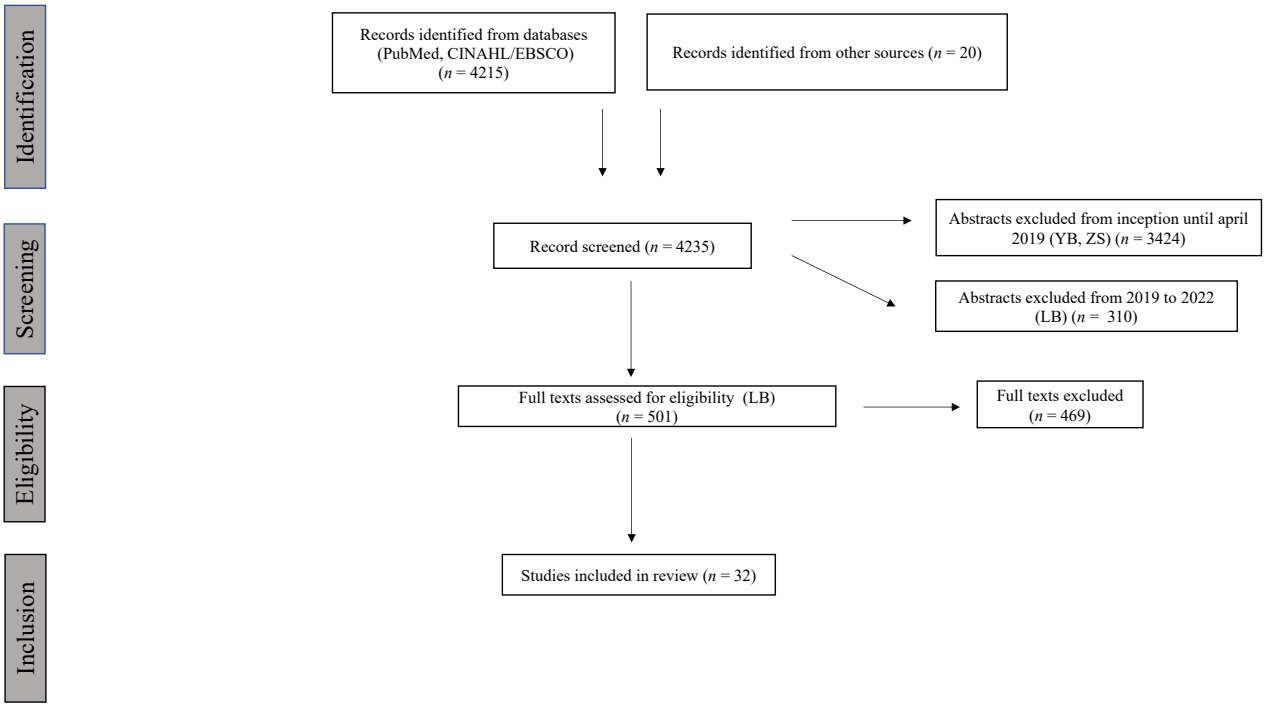


Table 1. Descriptive of included studies

Author, year of publication	Design	Nb of patients (nb of 65+)	Molecule & Dose	Medical Indication	Psychotherapy	Safety & tolerability	Efficacy
Anderson B., 2020	Open label study	18 (1 : 66 y.o.)	Psilocybin, D = 0,3 and 0,36 mg/kg	Gay-identified men with diagnosis of HIV prior to the clinical availability of protease inhibitors and Moderate-to-severe demoralization (DS-II score of ≥ 8/32.	Non-directive and supportive; 3 hours of individual psychotherapy, 12,15h of group psychotherapy (Brief Supportive Expressive Group Therapy (SEGT));, and one 8-hours individual psilocybin administration and 4 to 6 post-drug group therapy visits	No serious adverse event. Nausea (n = 1), self-limited, asymptomatic, severe hypertension in conjunction with anxiety (n = 4); self-limited, moderate hypertension (n = 8) moderate and severe anxiety reactions (n = 8), paranoia (n = 4), transient thought disorder (n = 1), post-traumatic stress flashbacks the following day (n = 1), severe anxiety 10 days after and relapse in methamphetamine use (n=1)	Clinically meaningful change in demoralization from baseline to end-of-treatment (mean difference -6,67 [SD 6,51]) and from baseline to 3-month follow-up (mean difference -5,78 [SD 6,01]) with a standardized effect size of Np2 = 0,47, 90% CI 0,21-0,60 for change over these three timepoints.
Bogenschutz, M. P., 2015	Open label study	10 (0)	Psilocybin; D1 = 0.3 mg/kg, D2 = 0.4 mg/kg	Alcohol dependance	MET (7 sessions) + 12 sessions (4 preparational and 8 integration sessions)	No serious adverse event, diarrhea, nausea, emesis (1 patient), headache, insomnia	Percent heavy drinking days decreased during weeks 5–12 relative to baseline (mean difference (SD) = 26.0 (22.4), 95% CI 8.7–43.2, t(8) = 3.477, p = 0.008) and percent drinking days also decreased during weeks 5–12 relative to baseline (mean difference (SD) = 27.2 (23.7), 95% CI 9.0–45.4, t(8) = 3.449, p = 0.009) after psilocybin session at week 4.
Bouso, J. C., 2008	Open label study	6 -expected 21- (0)	MDMA ; D = 50 to 75 mg	Chronic PTSD	Non-directive and supportive; 6 sessions 90-minutes (3 before, 3 after)	No serious adverse event, headache, sleepiness, fatigability	Not enough subjects to conclude due to political issues (see below in the *discussion* part)
Carhart-Harris, R. L., 2016	Open label study	12 (0)	Psilocybin; D1 = 10, D2 = 25 mg	Mild to severe MDD (HAM-D > 17)	Non-directive and supportive; 1 preparatory session with psychiatrist (4h), 1 debriefing session, then e-mail follow-up	No serious adverse event, transient nausea, transient confusion and headache, anxiety, transient and mild paranoia (2 patients)	Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference 11·8, 95% CI –9·15 to –14·35, p=0·002, Hedges' g=3·1) and 3 months (–9·2, 95% CI –5·69 to –12·71, p=0·003, Hedges' g=2) after high-dose treatment.

Carhart-Harris, R. L., 2021	Randomized, double-blind, controlled trial, in phase 2	59 (0)	Psilocybin; D = 25 mg	Mild to severe MDD	Non-directive and supportive; 2 preparational sessions, 2 drug session and 2 integrative sessions	No serious adverse event, less adverse effect than the escitalopram group	Mean (±SE) change from baseline in the score on the QIDS-SR-16 at week 6 was −8.0±1.0 in the psilocybin group and −6.0±1.0 in the escitalopram group (difference, −2.0; 95% confidence interval [CI], −5.0 to 0.9; P=0.17), indicating no significant difference between the trial groups in an ITT and per-protocol analysis.
Danforth, A. L., 2018	Randomized, double-blind, placebo-controlled, phase 2 single-site study	12 (0)	MDMA; G1: D1 = 75mg, D2 = 100mg; G2: D1 = 100mg, D2 = 125mg	Social Anxiety Disorder (SAD) in autistic population LSAS ≥ 60	Integrative psychotherapy (mindfulness and DBT); three 60- to 90-mins psychotherapy sessions, two drug sessions and three 60- to 90-minutes psychotherapy sessions	No serious adverse event, significant elevation of blood pressure, heart rate and body temperature, headache, anxiety, fatigue	Reduction in SAD symptoms as indicated by mean change in LSAS score from baseline to primary endpoint was significantly greater for the MDMA group than for the placebo group (t(9) = 2.451, P = 0.037, CI 1.92, 47.87). At 6-month follow-up, the decline in mean LSAS score from baseline was largest for the MDMA group compared to placebo group (t(9) = 2.454, P = 0.036, CI 1.92, 47.01).
Davis and al., 2021	Randomized, waiting list controlled clinical trial	24 (0)	Psilocybin; D1= 20 mg/70 kg; D2: 30 mg/70 kg	MDD	Non-directive and supportive; approx. 11 hours	No serious adverse event, significant elevation of diastolic blood pressure (no medical intervention needed), mild to moderate transient headache during the sessions (33%) or after (29%), challenging emotions and body experiences.	In the immediate treatment group, the mean (SD) GRID-HAMD scores were 22.9 (3.6) at baseline, 8.0 (7.1) at week 5, and 8.5 (5.7) at week 8. In the delayed treatment group, the mean (SD) GRID-HAMD scores were 22.5 (4.4) at baseline, 23.8 (5.4) at week 5, and 23.5 (6.0) at week 8. Effect sizes (Cohen d with 95% CI) and P values reflect the results of a 2-sample t test between the 2 groups at week 5 (Cohen d = 2.5; 95% CI, 1.4-3.5; P < .001) and week 8 (Cohen d =2.6; 95% CI, 1.5-3.7; P < .001).
Gasser, P., 2014	Randomized, double-blind, active placebo-controlled pilot study	11 (0)	LSD; D1 = 200 µg; active placebo = 20 µg	Anxiety associated with a life-threatening disease STAI > 40	Non-directive and supportive; 6 sessions (2 before, LSD session, 3 after)	No serious adverse event, secondary hypertension, vision blurred, moderate headache, hallucinations, mood change, dysphoric reaction, feeling cold.	At the 2-month follow-up, the STAI in reductions in trait anxiety (p = 0.033) with an effect size of 1.1, and state anxiety was significantly reduced (p = 0.021) with an effect size of 1.2.
Griffiths, R. R., 2016	Randomized, double-blind, cross-over trial	51(0)	Psilocybin; D = 22-30mg/70kg, Low dose (placebo-like) = 1-3mg/70kg	Potentially life-threatening cancer diagnosis and a DSM-V diagnosis of anxiety or mood symptoms	Non-directive and supportive; mean of 3 sessions before 1st dose, mean 2.7 meetings between and 2 meetings until the 6-month follow-up	No serious adverse event, transient psychological distress and discomfort, anxiety, transient episode of paranoid ideation, nausea and vomiting, transient elevation of	Significant response and symptom remission for the high dose group on depression GRID-HAMD-17 and anxiety HAM-A compared to the low dose group at week 5 (p<0.001) and maintained at 6 months follow-up.

						blood pressure, physical discomfort, headache post-session.	
Grob, C. S., 2011	Double-blind, placebo-controlled study	12 (0)	Psilocybin; D = 0.2 mg/kg	Acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, adjustment disorder with anxiety	Non-directive and supportive; 2 weeks prior to the first treatment session to up to 6 months after the second (including monthly calls)	No serious adverse event, mild but significant elevation of heart rate and diastolic blood pressure	STAI-trait anxiety subscale demonstrated a significant reduction in anxiety at 1 and 3 months after treatment. BDI revealed an improvement of mood that reached significance at 6 months; the POMS identified mood improvement after treatment with psilocybin that approached but did not reach significance.
Grof, S., 1973	Open-label study	31(4: 70, 72, 81, 81 y.o.)	LSD (D = 200-500 µg), DPT (D = 60-105 mg I.M.)	Emotional distress, physical pain, depression, anxiety, and psychological isolation associated with malignancy	Non-directive and supportive; « a real human encounter » several before and after 6 to 12h (average 9,75h) for 3 weeks	No serious adverse event, nausea, vomiting, fatigue, urinary and fecal incontinence (individuals w/ pelvic cancer)	Significant reduction in mean global index for depression, anxiety, pain, fear of death, isolation, management before and after psychedelic therapy; reduction mean score of the amount of narcotics non-significant. «Illustrations or indications of the therapeutic efficacy of psychedelic treatment with terminal cancer patients, rather than a conclusive statistical proof »
Grof, S., 1973	Open-label study	51(0)	DPT; 60 to 150 mg I.M. (C = 15 mg/cm3)	Alcohol dependance	Non-directive and supportive; several drug-free meetings (12 to 15 hours) before and 3 meetings after	**One serious adverse event: Brief psychotic episode** Readmission, treatment with antipsychotics with severe neurotic syndromes.	Significant change in POI from pre- to post-testing ($p<0,001$), significant in most measured parameters for MMPI, just some parameters in PEP and Benton visual retention test did not show significance. Significant improvement in abstinence at 6-month follow-up for 25 of the 47 individuals left (3 lost) and global adjustments and interpersonal adjustments.
Johnson, M. W., 2014	Open-label uncontrolled pilot study	15 (0)	Psilocybin; D_{low} = 20mg/70kg and D_{high} = 30mg/70kg	Tobacco addiction ≥ 10 cigarettes per day, multiples unsuccessful quit attempt and desire to quit	CBT (quit for life program), mindfulness, guided imagery exercise;	No serious adverse event. Elevated blood pressure, headache after the session, dysphoric subjective effects.	Biomarkers assessing smoking status, and self-report measures of smoking behavior demonstrated that 12 of 15 participants (80%) showed seven-day point prevalence abstinence at 6-month follow-up.
Kast, M., 1967	Open-label study	128 (undisclosed)	LSD; D = 100 µg	Pain and existential distress for patient suffering of a malignant disease with metastases, life expectancy ≤ 2 months	Non-directive and supportive; Daily visits the week before administration, during administration and daily for the 3 following weeks	No serious adverse event. Panic (5%), hallucinations (10%), visual distortions (55%), mild anxiety reactions (33%) amenable to psychotherapy	Pain and depression score reduction 3 hours after administration and lasted until 12 hours. No information about statistical significance.

Kurland, A., 1971	Randomized, double-blind, placebo-controlled study	135 (0)	LSD; D_{Low} = 50 µg and D_{High}= 450 µg	Alcohol dependance	Non-directive and supportive; preparative sessions (20h)	1 adverse event, reversed by conventional therapy, no detail.	Significant differences between high- (53% rehabilitated) and low-dose (33%) in global adjustment and in drinking behavior at 6-month follow-up (but not 12 and 18-month follow up).
Mc Cabe, O., 1972	Randomized, double-blind, controlled trial	85 (0)	LSD; D_{Low} = 50 µg and D_{High}= 350 µg	Psychoneurotic diagnosis	Non-directive and supportive; 20 h of preparation session, 12-14h long LSD session, 1 week hospitalization with several meeting with therapist after the session	1 adverse event, reversed by conventional therapy, no detail.	Group Therapy vs. High-Dose LSD: Of the thirty-three scales of the MMPI, EPI, and POI, fifteen scales showed significant between-group differences from pre- to post-treatment scores. Low-Dose LSD vs. High-Dose LSD: although the pre- and post-treatment scores on all tests showed a consistent change-trend in favor of high-dose vs. low- dose LSD therapy, only the Neuroticism (N) scale of the EPI demonstrated a statistically significant (p<0,05)
Mitchell J. M., 2021	Randomized, double-blind, controlled trial, in phase 3	91 (0)	MDMA; D = 80–180 mg	Severe PTSD	Non-directive and supportive; 12 sessions	**2 serious adverse events**: 2 participants in the placebo group with **suicidal ideation** and **suicidal behavior.** **9 adverse events of special interest (AESIs)**: 5 in the placebo group and 3 in the MDMA group reported of suicidal ideation and self-harm in the context of suicidal ideation and 1 cardiac event w/ irregular heartbeats and palpitations. Nausea, loss of appetite, transient elevation of systolic, diastolic blood pressure and heart rate, muscle tightness, hyperhidrosis and feeling cold	Mixed model repeated measure (MMRM) analysis of the de jure estimand (that is, the effects of the drug if taken as directed) showed a significant difference in treatment arms (n = 89 (MDMA n = 46), P < 0.0001, between-group difference = 11.9, 95% confidence interval (CI)= 6.3–17.4, d.f. = 71). MMRM sensitivity analysis of the de facto estimand (that is, the effects of the drug if taken as assigned, regardless of adherence) showed a significant difference in treatment arms (n = 90, P < 0.0001, d.f. = 72). Clinically significant improvement (a decrease of ≥10 points on the CAPS-5), loss of diagnosis (specific diagnostic measure on the CAPS-5), and remission (loss of diagnosis and a total CAPS-5 score ≤ 11) were each tracked.

Mithoefer, M. C., 2018	Randomized, double-blind, dose-response, phase 2 clinical trial	26 (0)	MDMA; D1 = 75 mg or D2 = 125 mg, active placebo = 30 mg	PTSD duration ≥ 6-months, CAPS-IV ≥ 50 and failure to respond or inability to tolerate previous pharmacotherapy or psychotherapy	Non-directive or client-directed psychotherapy; three 90-minutes sessions before and three after, daily calls for 7 days after	**1 serious adverse event possibly related to the drug:** Acute increase in premature ventricular contractions. 3 serious adverse event unrelated to the drug: suicidal ideation and MDD (1 patient), appendicitis. Significant elevation of systolic, diastolic BP and HR, headache, anxiety, muscle tension. Anxiety, insomnia, and fatigue in the following week.	At the primary endpoint, Significant greater decrease of CAPS-VI total score in groups 75mg and 125mg (mean change CAPS-IV total scores of –58·3 [SD 9·8] and –44·3 [28·7]; p= Compared with the 30 mg group. Cohen's d effect sizes were large: 2·8 (95% CI 1·19–4·39) for the 75 mg group and 1·1 (0·04–2·08) for the 125 mg group. 0·001) than the 30 mg group (–11·4 [12·7]).
Mithoefer, M. C., 2011	Randomized controlled pilot study	20 (0)	MDMA; 125 mg +/- optional supp. dose = 62.5 mg	DSM-V crime or war-related chronic and resistant PTSD CAPS ≥ 50 following at least 3 months of prior SSRI or SNRI w/ at least 6 months psychotherapy	Non-directive and supportive, hollotropic breathwork (Grof) and adapted for MDMA-assisted psychotherapy for PTSD; Two 90-minutes introductory sessions, four 90-minutes integrative sessions after each experimental session (= 1 the day after, three in the following weeks) and daily calls for 7 days after	No serious adverse event. Nausea, loss of appetite, dizziness, headache, anxiety, jaw tightness, impaired balance, feeling cold. Irritability, low mood and fatigue the week after.	MDMA-assisted psychotherapy compared with the same psychotherapy with inactive placebo produced clinically and statistically significant improvements in PTSD symptoms as measured by standard symptom scales, immediate and maintain throughout time (2-month follow-up). The rate of clinical response was 10/12 (83%) in the active treatment group versus 2/8 (25%) in the placebo group.
Monson C. M., 2020	Uncontrolled study	6 couples = 6 patients + 6 partners (0)	MDMA; D1 = 75 mg; D2 = 100 mg +/- half dose after 1,5 h	Severe PTSD or partner of a person with severe PTSD	CBCT; 3 preparatory sessions and 5 integrative sessions (2 after the 1ST MDMA session, 3 after the second)	No serious adverse event. Diminished appetite, headache, anxiety, jaw tightness.	Growth curve modelling revealed significant and sustained improvements in CAPS (B = −4.64, p < .001), with d = 1.88–2.25 at posttreatment and follow-ups. All but one patient showed a sustained remission in their clinician-assessed PTSD diagnosis. Self- (B = −8.14, p < .001) and partner-rated (B = −5.90, p < .001) PTSD symptoms significantly improved, with d = 2.72–3.59 for patients, and 1.85–2.72 for partners at post-treatment and follow-ups, respectively

Moreno, F. A., 2006	Double-blind, placebo-controlled study	9 (0)	Psilocybin; D= 25, 100, 200 or 300 µg/kg	DSM-V Obsessive Compulsive disorder diagnosis w/ at least one adequate treatment trial with SRI, YBOCS score [18,36] and 1 well-tolerated exposure to indole-based psychedelics	None, presence of one male and female sitter during the drug sessions	No serious adverse event. Transient high blood pressure.	Marked decreases in OCD symptoms of variable degrees were observed in all subjects during 1 or more of the testing sessions (23%–100% decrease in YBOCS score). Repeated measures analysis of variance for all YBOCS values revealed a significant main effect of time on Wilks lambda ($F = 9.86$, $df = 3,3$; $p = .046$), but no significant effect of dose ($F = 2.25$, $df = 3,3$; $p = .261$) or interaction of time and dose ($F = 0.923$, $df = 9,45$; $p=.515$).
Oehen, P., 2013	Randomized, double-blind, active placebo-controlled trial	12 (0)	MDMA; D = 125 mg +/- 62.5 mg of MDMA 2-2.5h after, active placebo = 25 mg +/- 12,5 mg	DSM-IV PTSD with treatment-resistant symptoms CAPS ≥ 50 and having previously undergone at least 6 months of psychotherapy and 3 months of treatment with an SSRI	Non-directive and supportive (MDMA psychotherapy); 2 prepatory sessions, 3 integrative sessions +/- additional sessions if necessary (max. 4) and 12-month follow-up.	No serious adverse event. Loss of appetite, headache, dizziness, impaired gait/balance, moderate insomnia, restlessness tight jaw, thirst, feeling cold.	Significant effect of time and group in the Full dose group; A comparison of the safety profiles between 25 mg and 125 mg doses did support that the 125 mg dose was associated with more reactions, in general. Efficacy failed to reach statistical significance ($p = 0.066$) as measured by the primary outcome measure, the CAPS; whereas self-assessment of the subjects' PTSD symptoms, as measured by the self-reporting questionnaire PDS showed a significant reduction ($p = 0.014$).
Osorio Fde, L., 2015	Open-label uncontrolled trial	6 (0)	Ayahuasca; D = 120-200 mL	Recurrent MDD	None	No serious adverse event. Vomiting (50%), non-significant elevation of BP, effect on thoughts and sensory perception mild and short-lived.	Significant decrease of HAMD at day 1 (62%), day 7 and day 21 and significant decrease of MADRS at 180 minutes, D1, D7, D14 and D21 compared to baseline.
Ot'alora, G. M., 2018	Randomized phase 2 controlled trial	28 (1 : 66 y.o.)	MDMA; D = 40, 100 or 125 mg +/- half dose 90 mins later	Chronic PTSD, CAPS-IV ⩾50 and failed to respond to at least one course of pharmacotherapy and/or psychotherapy	Non-directive and supportive (curious, open, and attentive to the participant's developing experience; sense of safety and communicating trust); three 90-minutes preparatory sessions, daily calls for 7 days and three 90-minutes integrative sessions	No serious adverse event. Significant elevation of HR in 125 mg group, headache, dizziness, anxiety, low mood, ruminations, jaw clenching/thigh jaw, muscles tension, insomnia, fatigue	In the ITT set, the active groups had the largest reduction in CAPS total scores at the primary endpoint, with mean (SD) changes of −26.3 (29.5) for 125 mg, −24.4 (24.2) for 100 mg, and −11.5 (21.2) for 40 mg, though statistical significance was reached only in the per protocol set ($p=0.03$). Posttraumatic stress disorder symptoms remained lower than baseline at 12-month follow-up ($p<0.001$) with 76% (n=25) not meeting posttraumatic stress disorder criteria.

Pahnke, W., 1969	Open-label study	22 (undisclosed)	LSD; 200 to 400 µg (IM/IV)	Depressive reaction associated with the patient's physical condition but also anxiety, psychological withdrawal, and physical pain	Non-directive and supportive; preparatory session including group and family sessions (approx. 10h), intensive help toward integrating the experience after drug session	No serious adverse event. No description of adverse event	Meaningful positive change in two-thirds of the patients and dramatic improvement for 6 of these 14 patients (5 of them were 'peakers'). No information about statistical significance.
Palhano-Fontes, F., 2019.	Randomized placebo-controlled trial	29 (0)	Ayahuasca, D = 0.36 mg/kg	Treatment-resistant unipolar major depressive disorder, moderate-to-severe depressive episode at screening (HAM-D⩾17)	None, one debriefing just after the cessation of the drug effects	No serious adverse event. Transient nausea, vomiting, transient headache, transient anxiety, restlessness.	Significant between-groups difference at day 7 ($F1 = 6.31$; $p = 0.019$), and patients treated with ayahuasca showed significantly reduced severity when compared with patients treated with placebo. Effect of time.
Ross, S., 2016	Double-blind, placebo-controlled, crossover trial	29 (9: 66, 71, 67, 67, 65, 75, 69, 68, 65)	Psilocybin, D = 0,3 mg/kg	Anxiety and depression symptoms in patients with life-threatening cancer diagnoses	Non-directive and supportive, historical model developed by Stanislav Grof that included the following components: Preparatory Psychotherapy, Medication Dosing Sessions, and Post-dosing Integrative Psychotherapy; three 2-hours preparatory sessions and six 2-hours integrative sessions (three after each of the drug sessions)	No serious adverse event. Nausea, non-significant elevation of BP and HR, headaches/migraines, anxiety, transient near-psychotic symptoms	For all primary outcome measures (HADS T, HADS A, HADS D, BDI, STAI S, STAI T), the psilocybin first group demonstrated significant within-group reductions (compared to baseline at each post-baseline assessment point) in anxiety and depression immediately after receiving psilocybin. These reductions remained significant at each time point, including the final point at 26 weeks post-dose 2 (approximately 8 months), post-psilocybin dosing.
Richards, W., 1972	Open-label uncontrolled pilot study	31 (1 or +: max. 81 y.o.)	LSD; D = 300 to 500 µg, mean 323 µg I.M.	Physical pain, depression, anxiety, or physical isolation associated with malignancy	Non-directive and supportive; 6 to 12 hours of prepatory and integration sessions	Undisclosed	Out of 36 differences of mean scores, only 3 did not show statistical significance or a strong positive trend.

Richards, W., 1977	Open-label uncontrolled study	34 (1: 71 y.o.)	DPT; D = 75 to 127.5 mg I.M., dosage was determined by the judgement of the therapist, considering body weight and psychological resistance	Psychological distress, defined as depression, anxiety and/or psychological isolation associated with malignancy	Supportive and Guided Affective Imagery; 20,5 hours of psychotherapy	Undisclosed	None of the changes from pre- to post-therapy on the 12 POI scales reached statistical significance for the group of 15 non-peakers on whom POI data were available. In contrast, nine of the same scales reached statistical significance for the group of 13 peakers who had completed the POI, all changes being in the direction of improved self-actualization.
Sanches, R. F., 2016	Open-label study	14 (0)	Ayahuasca, D = 2.2 ml/kg	Recurrent MDD	None	No serious adverse event. Vomiting (47%).	Significant HAM-D and MADRS score decreases from 80 to 180 minutes ($P < 0.01$) and from D1 to D21 ($P = 0.000$)
Savage, C., 1973	Double-blind, placebo-controlled study	74 (0)	LSD; D = 300 µg to 450 µg	Narcotic addiction in a carceral population	Non-directive and supportive; 24 hours of preparatory psychotherapy and integration sessions during the week after the drug session	Undisclosed	9 (25%) of the 36 subjects in the treatment group maintained total abstinence from narcotics drugs for at least one years opposed to two (5%) of the 37 in the control group ($p<0.05$)
Wolfson F., 2020	Double-blinded, randomized, placebo-controlled design with an additional open-label crossover	18 (0)	MDMA, D = 125 mg	Anxiety from a life-threatening illness (LTI)	Undisclosed; nine 60- to 90-min non-drug psychotherapy sessions; three preparing participants for the first experimental session and three for integration after each experimental session and 8 hours psychotherapy associated during the drug session	No serious adverse event. Headache, significant elevated body temperature, thirst, jaw clenching/tight jaw, dry mouth and perspiration.	At the primary endpoint, the MDMA group had a greater mean (SD) reduction in STAI-Trait scores, −23.5 (13.2), indicating less anxiety, compared to placebo group, − 8.8 (14.7); results did not reach a significant group difference ($p = .056$). Hedges'g between-group effect size was 1.03 (95% CI: − 5.25, 7.31).

BDI/ BDI-II = Beck Depression Inventory/-II, CAPS = Clinician-Administered PTSD Scale, DBT = Dialectical behavioral therapy, GRID-HAMD = GRID-Hamilton Depression Rating Scale, HAM-D = Hamilton Rating Scale for Depression, ITT = intention-to-treat analysis, LSAS = Leibowitz Social Anxiety Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MET = Motivational Enhancement Therapy, MMPI = Minnesota Multiphasic Personality Inventory, PEP = Psychiatric Evaluation Profile, POI = Personal Orientation Inventory, POMS = Profile of Mood States, PP = per protocol, QIDS = Quick Inventory of Depressive Symptomatology, STAI = State-Trait Anxiety Inventory, VAS = Visual Analog Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale

NB: Peakers are the patients who went through a Peak Experience (ego dissolution, loss of boundaries, mystical experience)

Table 2. Primary and secondary outcomes assessing efficacy in specific medical indications.

		Primary outcomes	Secondary outcomes	Altered consciousness scores
MDD, "depressive reaction" (28)		QIDS (2), GRID-HAMD, BPRS (2), HAM-D (3), MADRS (2), YMRS, BPRS, CADSS	BDI (2), STAI-T, SHAPS, HAM-D (2), MADRS (3), GAF, FS, BEAQ, WSAS, SHAPS, WEMWBS, SIDAS, PRSexDQ, LEIS, QIDS-SR (Self-Rated), MMPI, EPI, POI, YMRS	11D-ASC, Emotional Breakthrough Inventory, BPRS, CADSS, BPRS, YMRS, HRS, MEQ30
PTSD		CAPS-5/IV (6), SSSPTSD (Spanish version of PSS), PCL-5, PDS	Semi-structural Interview about sexual assault, STAI, BDI and BDI-II (3), HAM-D, MFS-III, MS, SE/R, HAq, SDS, PSQI (2), PTGI, NEO-PI-R, DES-II (2), GAF, IES-R, SCL-90-R, neuropsychological testing	HRS, UKUSSE, subjective unit of distress
Anxiety		LSAS (Social Anxiety Disorder), YBOCS and VAS (OCD)	BDI-II (2), PSS, IRI, RSES, STAI (2), TAS-20, TASIT, ERQ,	HRS
Serious illness-related distress		STAI form X, GRID-HAM-D-17, HAM-A, SIGH-A, persisting effects questionnaire, BDI (2), POMS, STAI (S/T) (3), hetero-evaluation of pain and mood changes, hetero-evaluation (physicians, nurses, family and LSD therapist) on depression, anxiety emotional tension, psychological isolation, HADS T/A/D, HADS A, HADS D, hetero-evaluation by Pahnke and Richard's scale, POI, MMPI, Mini-Mult,	EORTC-QLQ-30, SCL-90-R, HADS, BDI/-II (2), HADS, STAI, POMS, BSI, MQOL, LOT-R, LAP-R (2), Death Transcendence Scale, Purpose in Life Scale, FACIT-(Sp/Swb) (3), Spiritual-Religious Outcome Scale, Faith Maturity Scale, BPRS (2), Hetero-evaluation of approach to illness and death, sleep patterns, visual disturbances, the amount of drug consumed to control physical pain (2), DEM, HAI, DAS, DTS, WHO-bref, PTGI (2), FFMQ, PSQI, MADRS, GAF, SCS, DAP	Monitor Rating Scale, 5D-ASC, hetero-evaluation of hallucinations and fear and panic reactions, MEQ, PEQ, PERF
		DS-II, Pahnke and Richard's scale	CESD-R, CGI-S, MQoL-R, STAI, narcotic consumption (pain),	
Addictology	Alcohol	Drinking days and heavy drinking days, MMPI, POI, PEP, Raven progressive matrices and Benton visual retention test, Global Adjustment and Drinking behavior scale	POMS, Social history questionnaire, MMPI, POI, PEP, EPI	HRS, MEQ, G-ASC, SOCQ (2), Visual effects questionnaire, post-session headache interview, Mysticism scale, persisting Effects Questionnaire
	Tobacco	Smoking biomarkers	TLFB, QSU, SASE, FTCD, QSU, SASE, WSWS	
	Narcotics	Abstinence at 6- and 12-month follow-up	Global adjustment rating scale	

5/11D/G-ASC = 5/11-dimension/Summary Altered States of Consciousness scale, BDI/ BDI-II = Beck Depression Inventory/-II, BEAQ = Brief Experiential Avoidance Questionnaire, BPRS= Brief Psychiatric Rating Scale, BSI = Brief Symptom Inventory, CADSS = Clinician Administered Dissociative States Scale, CAPS-IV/5= Clinician-Administered PTSD Scale, CESD-R = Center for Epidemiological Studies Depression Scale-Revised, CGI-S = Clinical Global Impressions scale, C-SSRS = Columbia Suicide Severity Rating Scale, DAP = Death Attitudes Profile, DAS = Death Anxiety Scale, DEM = Demoralization scale, DES-II = Dissociative Experiences Scale-II, DS-II = Demoralization Scale-II, DTS = Death Transcendence Scale, EORTC-QLQ-30 = European Cancer Quality of Life Questionnaire 30-item version 1.0, EPI = Eysenck Personality Inventory, ERQ = Emotion Regulation Questionnaire, FFMQ = Five-Facet Mindfulness Questionnaire, FS = Flourishing Scale, FACIT-Sp/Swb = Functional Assessment of Chronic Illness Therapy-Spiritual/Social Well-Being, FTCD = Fagerström Test for Cigarette

Dependence, GAF = Global Assessment of Functioning, GRID-HAMD = GRID-Hamilton Depression Rating Scale, HADS T/A/D = Hospital Anxiety and Depression Scale Total/Anxiety/Depression, HAI = Hopelessness Assessment and Illness, HAM-A = Hamilton Anxiety Rating Scale, HAM-D = Hamilton Rating Scale for Depression, HAq = Penn Helping Alliance Questionnaire, HRS = Hallucinogen Rating Scale, IES-R = Impact of events scale revisited, IRI = Interpersonal Reactivity Index, LAP-R = Life Attitude Profile-Revised, LEIS = Laukes Emotional Intensity Scale, LOT-R = Revised Life Orientation Scale (optimism), LSAS = Leibowitz Social Anxiety Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MEQ-30= Pahnke-Richards Mystical Experience Questionnaire, MMPI = Minnesota Multiphasic Personality Inventory, MFS-III = Modified Fear Scale, MQOL/MQoL-R = McGill Quality of Life Questionnaire/Revised, MS = Maladjustment Scale, NEO-PI-R = Neuroticism-Extroversion-Openness Personality Inventory-Revised, PCL-5 = PTSD checklist for DSM-5, PDS = Posttraumatic Diagnostic Scale, PEP = Psychiatric Evaluation Profile, PEQ = Psychedelic Experience Questionnaire, PERF = Peak Experience Rating Form, POI = Personal Orientation Inventory, POMS = Profile of Mood States, PRSexDQ = Psychotropic-Related Sexual Dysfunction Questionnaire, PSQI = Pittsburg Sleep Quality Index, PSS = PTSD Symptom Scale, PTGI = Post-Traumatic Growth Inventory, QIDS = Quick Inventory of Depressive Symptomatology, QSU = Questionnaire on Smoking Urges, RSES = Rosenberg Self-Esteem Scale, SASE = Smoking Abstinence Self-Efficacy scale, SCL-90-R = Symptom Check-List-90-R, SCS = Self-Compassion Scale, SDS = Sheehan Disability Scale, SE/R = Rosenberg Self-Esteem scale, SHAPS = Snaith Hamilton Anhedonia Pleasure Scale, SIDAS = Suicidal Ideation Attributes Scale, SIGH-A = Structured Interview Guide for the Hamilton Anxiety Scale, SOCQ = States of Consciousness Questionnaire, SSSPTSD = Severity of Symptoms Scale for Post-traumatic Stress Disorder, STAI = State-Trait Anxiety Inventory, TAS-20 = Toronto Alexithymia Scale, TASIT = Awareness of Social Inference Test, TLFB = Timeline follow back, UKUSSE = UKU Scale of Secondary Effects, VAS = Visual Analog Scale, WEMWBS = Warwick-Edinburgh Mental Wellbeing Scale, WHO-bref = World Health Organization Qualify of Life scale brief version, WSAS = Work and Social Adjustment Scale, WSWS = Wisconsin Smoking Withdrawal Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale, YMRS = Young Mania Rating Scale

Table 3. Adverse events for elderly patients included in clinical trials

Patient	Treatment	Age	Dose	AE	Reportable event ?	Severity	Relationship to Drug	Actions taken	Outcome	Comments
1	Psilocybin	66	0,3 mg/kg	Elevated systolic BP (142/75) at 120 mins after dosing	No	1= Mild	2 = Probable	4 = None	1 = Recovered/Resolved	BP was repeated until it was <140/90
2	Psilocybin	71	0,3 mg/kg	Elevated systolic BP (143/87) at 10 mins pre dosing	No	1= Mild	5 = Not related	5 = Other (comment)	1 = Recovered/Resolved	
				Elevated systolic BP (161/87) at 180 mins after dosing	No	2 = Moderate	2 = Probable	5 = Other (comment)	1 = Recovered/Resolved	BP was repeated until it was <140/90
				Elevated systolic BP (158/88) at 240 mins after dosing	No	2 = Moderate		5 = Other (comment)	1 = Recovered/Resolved	BP was repeated until it was <140/90
				Elevated systolic bp (149/77) at 300 mins after dosing	No	2 = Moderate	2 = Probable	5 = Other (comment)	1 = Recovered/Resolved	BP was repeated until it was <140/90
				Breakthrough Pain	No	3 = Severe	5 = Not related	1 = Concomitant Medication addition or change	1 = Recovered/Resolved	240 mins after dosing, subject experience breakthrough pain. Took one dose of percocet (5mg/325mg)
				Nausea	No	2 = Moderate	5 = Not related	4 = None	1 = Recovered/Resolved	Lasted 2 hours. Nausea previously experiences by subject after using percocet
				Vomiting	No	2 = Moderate	5 = Not related	5 = Other (comment)	1 = Recovered/Resolved	AE occurred after subject was discharged from site
				Vasovagal Syncopal Event	No	3 = Severe	4 = Unlikely	5 = Other (comment)	1 = Recovered/Resolved	Pt brought to Bellevue ER. Discharged same day. Not a SAE as per the NYU IRB.
3	Psilocybin	67	0,3 mg/kg	Elevated BP (152/92) at 60 mins after dosing	No	3 = Severe	2 = Probable	4 = None	1 = Recovered/Resolved	BP was repeated until it was <140/90
				Elevated BP (156/98) at 90 mins after dosing	No	3 = Severe	2 = Probable	4 = None	1 = Recovered/Resolved	BP was repeated until it was <140/90
				Elevated BP (146/96) at 120 mins after dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	BP was repeated until it was <140/90
				Elevated systolic BP (148/90) at 180 mins after dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	BP was repeated until it was <140/90

4	Psilocybin	67	0,3 mg/kg	Elevated BP (143/94) at 90 mins post-dosing	No	1 = Mild	2 = Probable	4 = None	1 = Recovered/Resolved	
				Elevated BP (147/93) at 120 mins post-dosing	No	1 = Mild	2 = Probable	4 = None	1 = Recovered/Resolved	
				Elevated BP (142/93) at 180 mins post-dosing	No	1 = Mild	2 = Probable	4 = None	1 = Recovered/Resolved	
				Elevated diastolic BP (140/91) at 240 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	
				Elevated systolic BP (152/90) at 360 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	BP was repeated until it was <140/90
5	Psilocybin	65	0,3 mg/kg	Anxiety (Transient)	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Occurred at 9:45am, about 45 minutes post pill ingestion. Anxiety episode lasts about 3-4 minutes before patient reported being calm and feeling in control of her experience.
				Elevated BP (151/95) at 60 mins post-dosing	No	1 = Mild	2 = Probable	4 = None	1 = Recovered/Resolved	
				Elevated systolic BP (146/84) at 90 mins post-dosing	No	1 = Mild	2 = Probable	4 = None	1 = Recovered/Resolved	
				Elevated systolic BP (151/88) at 120 mins post-dosing	No	1 = Mild	2 = Probable	4 = None	1 = Recovered/Resolved	
				Nausea	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Started 30 mins post-dosing and last approx. 3 hours It was resolved without sequelae.
				Upper GI Gas	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Started 30 mins post-dosing and lasted 24 hours. It was resolved without sequelae.
6	Psilocybin	75	0,3 mg/kg	Elevated diastolic BP (134/98) at 60 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (153/89) at 90 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Paranoid Ideations (Transient)	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Transient paranoid ideations, started around 11:00am and last for about 30 minutes.

				Elevated BP (155/98) at 120 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated BP (155/98) at 180 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated BP (142/93) at 240 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated BP (152/95) at 300 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Ocular Migraine	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Began at night, post-dosing session. No pain. Lasted 30 mins and resolved without sequelae.
7	Psilocybin	69	0,3 mg/kg	Elevated systolic BP (145/68) at 30 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (149/70) at 60 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (167/75) at 90 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (173/83) at 120 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (185/79) at 180 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (186/84) at 240 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (150/90) at 300 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Transient experience of Thought Disorder	No	3 = Severe	2 = Probable	4 = None	1 = Recovered/Resolved	Pt had transient symptoms of a thought disorder. No symptoms of paranoia but was visibly restless and uncomfortable, and unable to respond through language to the therapists' attempts to make a verbal connection with her. Began approximately 12 PM and resolved fully by 5 PM. When she became verbal again, the pt reported having

										experienced no paranoid symptoms, nor any subjective distress while under the effects of the study medication
				Community Acquired Pneumonia (CAP)	No	3 = Severe	5 = Not related	4 = None	1 = Recovered/Resolved	Acquired 4 days post-dosing. Resolved completely with antibiotics (levofloxacin 750mg/day) on 6.8.13
8	Psilocybin	68	0,3 mg/kg	Elevated BP (142/93) at 60 mins post-dosing	No	2 = Moderate	1= Definite	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated BP (158/98) at 90 mins post-dosing	No	2 = Moderate	1= Definite	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (147/88) at 180 minutes post dosing	No	2 = Moderate	1= Definite	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Headache	No	2 = Moderate	1= Definite	4 = None	1 = Recovered/Resolved	Began morning after dosing. Resolved after taking 2 tablets of Excedrin. Resolved fully by end of day.
9	Psilocybin	65	0,3 mg/kg	Elevated systolic BP (150/90) at 90 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated BP (157/94) at 180 minutes post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (141/68) at 240 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
				Elevated systolic BP (148/83) at 300 mins post-dosing	No	2 = Moderate	2 = Probable	4 = None	1 = Recovered/Resolved	Resolved without sequelae.
10	Psilocybin	66	27 mg	Hypertension	No	1 = Mild			1 = Recovered/Resolved	
				Anxiety	No	1 = Mild			1 = Recovered/Resolved	
				Headache	No	1 = Mild			1 = Recovered/Resolved	During post-medication visit

Patients from 1 to 9 were included in Ross study in 2016, patient 10 was included in Anderson study 2020. (38,50)

Search algorithm

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR case report[pt] OR systematic[sb] OR metaanalysis[ti] OR meta-analysis[ti] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])) AND ("Hallucinogens"[Mesh] OR hallucinogen OR psychotomimetic OR psychedelic OR MDMA OR Methylenedioxymethamphetamine OR LSD OR "Lysergic acid diethylamide" OR psilocybin OR dipropyltryptamine OR DPT OR DMT OR dimethyltryptamine OR (mushroom AND hallucinogen*)) AND ("Stress Disorders, Post-Traumatic"[Mesh] OR "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Pain"[Mesh] OR "Alcoholism"[Mesh] OR "Substance-Related Disorders"[Mesh] OR "Tobacco Use Disorder"[Mesh] OR ptsd OR post-traumatic OR posttraumatic OR depression OR depressive OR pain OR alcoholism OR "alcohol use" OR "alcohol abuse" OR "drug abuse" OR "drug addiction" OR "drug use" OR "tobacco" OR nicotine OR distress OR cancer OR “end of life” OR “terminal care” OR “palliative care”)

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BOUCHET Lisa 2022 TOU3 1648

Prévalence des personnes âgées dans la recherche clinique sur les thérapies assistées par les psychédéliques : Une revue systématique de la littérature

Avant-propos. La littérature scientifique actuelle suggère une efficacité des thérapies assistées par les psychédéliques dans plusieurs indications psychiatriques. Elle concerne majoritairement une population jeune. L'efficacité et la tolérance chez la personne âgée dans le cadre d'études contrôlées restent largement inconnues.
Objectif. Déterminer la prévalence des personnes âgées inscrites dans les essais cliniques sur les psychédéliques et explorer les données de sécurité dans cette population.
Méthode. Nous avons entrepris une revue systématique de la littérature en respectant les recommandations PRISMA 2020. Nous avons inclus toutes les études cliniques, publiées en anglais ou en français, utilisant des substances psychédéliques (psilocybine, DMT, LSD, MDMA, ayahuasca and ibogaïne) pour traiter des troubles psychiatriques. La recherche a été réalisée sur les bases de données MEDLINE, PSYCHINFO et EMBASE.
Résultats. 4235 abstracts ont été évalués, dont 501 articles complets, l'inclusion finale contient 32 articles. Sur les 1103 patients inclus, au moins 17 ont plus de 65 ans, soit une prévalence d'environ 1.5 %. Aucun effet indésirable grave associé aux psychédéliques n'a été rapporté dans cette population.
Conclusion. À ce jour, les personnes âgées ont largement été exclues de la recherche clinique sur les thérapies assistées par les psychédéliques. De nouveaux travaux évaluant la tolérance et l'efficacité de ces thérapies dans cette population présentant des spécificités liées à l'âge et des comorbidités fréquentes semblent nécessaires.

TITRE EN ANGLAIS: Prevalence of Older Adults in Psychedelic-Assisted Therapy trials:
A Systematic Review

DISCIPLINE ADMINISTRATIVE: Psychiatrie

MOTS-CLÉS: Psychedelic, Psilocybin, LSD, MDMA, Ayahuasca, DMT, Older Adults, Elderly, Palliative Care, Psychiatry, Demoralization, Existential Distress, PTSD, MDD, Anxiety

INTITULÉ ET ADRESSE DE L'UFR OU DU LABORATOIRE :
Université Toulouse III-Paul Sabatier
Faculté de médecine Toulouse-Purpan,
37 Allées Jules Guesde 31000 Toulouse

Directeurs de thèse : Pr Antoine YRONDI et Dr Yvan BEAUSSANT