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Review article

Registered clinical studies investigating psychedelic drugs for psychiatric disorders

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ABSTRACT

Psychedelics are a hallucinogenic class of psychoactive drugs with the primary effect of activating non-ordinary states of consciousness. Due to the positive preliminary findings of these drugs in the treatment of psychiatric disorders, the number of registered clinical studies has risen significantly. In this paper, clinical studies registered on clinicaltrials.gov that evaluate the treatment of any psychiatric disorder with psychedelics (excluding ketamine) are summarized and analyzed. 70 registered studies were identified from a clinicaltrials.gov search on December 3, 2020. The majority of studies aim to investigate methylenedioxymethamphetamine (MDMA) (45.7%) and psilocybin (41.4%). Studies evaluating ayahuasca, lysergic acid diethylamide (LSD), ibogaine hydrochloride, salvia divinorum, 5-MeO-DMT and DMT fumarate were less common at 1.4%, 4.2%, 2.8%, 1.4%, 1.4% and 1.4% of total registered studies, respectively. Most of the studies on MDMA, psilocybin, ayahuasca and salvia divinorum investigated their therapeutic effect on post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). LSD was investigated for MDD, anxiety, and severe somatic disorders and ibogaine hydrochloride was investigated for substance and alcohol use disorders. 5-MeO-DMT and DMT fumarate were both investigated for MDD. Only 21/70 registered studies had published results with the majority not yet completed. In view of the large number of ongoing studies investigating psychedelics, it is imperative that these studies are considered by researchers and stakeholders in deciding the most relevant research priorities for future proposed studies.

1. Introduction

Psychedelics, also known as serotonergic hallucinogens, are among the hallucinogenic class of drugs and can exert profound effects on the brain and behavior via serotonin receptor mechanisms (Kyzar et al., 2017; Nichols, 2016). Psychedelic substances have predictable psychoactive properties that can influence perception, mood and cognition (Nichols, 2016).

Psychedelics is a broad category with mechanistically dissimilar agents. Based on pharmacological profiles and chemical structures, psychedelics can be divided into four classes: classic psychedelics (serotonin 2A [5-HT2A] receptor agonists), empathogens or entactogens (mixed serotonin and dopamine reuptake inhibitors and releasers), dissociative anesthetic agents (N-methyl-D-aspartate [NMDA] antagonists) and atypical hallucinogens, which affect multiple neurotransmitter systems (Reiff et al., 2020). Lysergic acid diethylamide (LSD), psilocybin, ayahuasca and N–N-dimethyltryptamine (DMT) (including 5-MeO-DMT and DMT fumarate) are considered classic psychedelics, salvia divinorum and ibogaine hydrochloride are classified as atypical psychedelics and methylenedioxymethamphetamine (MDMA) is considered an empathogen (Araujo et al., 2015; Reiff et al., 2020). Psychedelics can produce a wide range of experiential states, including feelings of boundlessness, unity and bliss, and anxiety-inducing experiences such as loss of ego-control and panic. Experience varies depending on the individual taking the drug, their expectations, the setting in which the drug is taken and the drug dose (Carhart-Harris et al., 2017;

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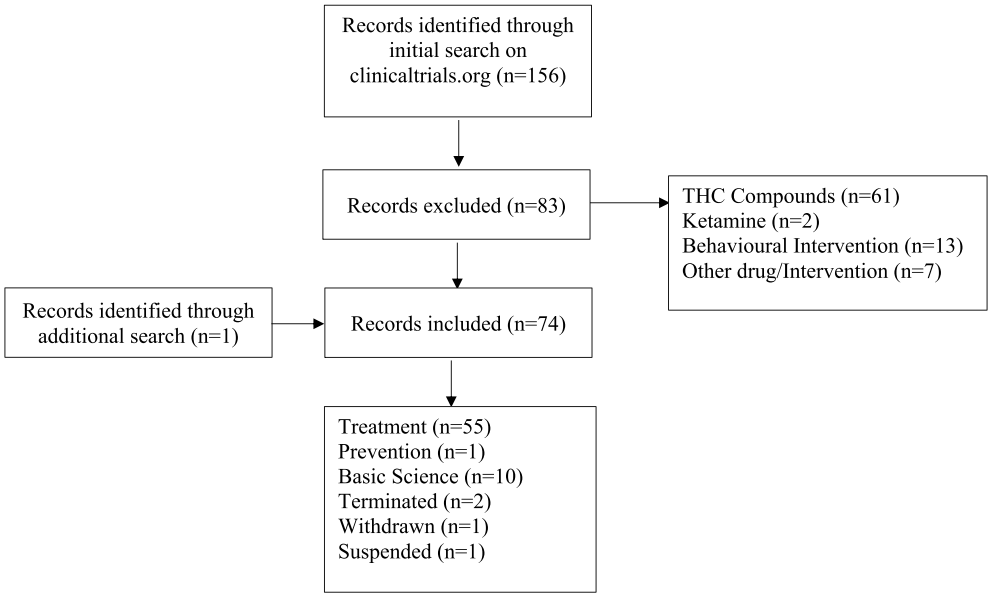

Fig. 1. Study selection schema.

Fischer, 1968). A detailed psychopharmacological profile of these psychedelics is beyond the scope of this review.

Due to their psychopharmacological properties, in the 1950's there was a surge of scientific interest in the therapeutic effect of psychedelics, such as LSD, for the treatment of psychiatric disorders. Throughout the 1950's and into the 1960's, researchers explored the benefits of LSD for conditions such as anxiety, depression and addiction. In 1966, LSD was deemed a schedule one drug (drugs with no currently accepted medical use and high potential for abuse) which led to a halt in psychedelic research (Sessa, 2016).

Between the 1980s and 1990s there were a number of trials investigating psilocybin and MDMA for psychiatric disorders such as anxiety and schizophrenia (e.g. Battaglia et al., 1988; Greer and Tolbert, 1986; Vollenweider et al., 1998). That said, within the past two decades there has been a substantial increase in research regarding the therapeutic effects of psychedelic substances. Notably, a surplus of research has focused on the therapeutic benefits of psychedelics when used in conjunction with psychotherapy (Sessa et al., 2019). In addition to LSD, MDMA and psilocybin, hallucinogens like ayahuasca and salvia are receiving attention in the field of psychiatry. Not only are these psychedelic substances receiving attention for randomized controlled trials, but they are also being recognized to have valuable clinical use, with four palliative care patients and one non-palliative patient receiving psilocybin exemptions this year in Canada (CTV News, 2020).

Numerous clinical studies have investigated the benefits of MDMA-assisted psychotherapy, often as a proposed treatment for post-traumatic stress disorder (PTSD). The findings thus far are promising, as multiple studies have found that as few as two MDMA-assisted psychotherapy sessions successfully reduced symptoms in patients with treatment-resistant PTSD, with patients maintaining remission status up to six years post-treatment (Sessa et al., 2019). Likewise, findings from a recent review indicate that psilocybin-assisted therapy successfully reduced depression and anxiety symptoms and increased abstinence rates in addiction, with individual studies having robust effect sizes (Hedge's $g > 2$) (Thomas et al., 2017). Similar findings have been reported with salvia, ibogaine and ayahuasca (Breeksema et al., 2020; Domínguez-Clavé et al., 2016). Moreover, clinical studies investigating the therapeutic effects and acute and long-term safety of these drugs have shown reliable safety and tolerability profiles (dos Santos et al., 2018).

Given the promising therapeutic effects and safety profile of psychedelics, there are numerous *ongoing* studies examining a range of psychedelic agents in the treatment of psychiatric disorders. The aim of the current analysis is to systematically identify all registered clinical studies investigating psychedelics for psychiatric disorders, including ongoing studies. Ketamine was excluded from the current analysis as these registered studies have been recently reviewed separately by our group, given the fundamental mechanistic differences (NMDA antagnoism) compared to the psychedelics reviewed herein, primarily focusing on serotonergic hallucinogens (Peyrovian et al., 2020). The results of this analysis are intended to provide investigators and other stakeholders with a comprehensive summary of psychedelic-related research questions likely to be answered in the near future. The results from the current review will also highlight key areas that are not currently being addressed in order to inform future research. Of note, the current analysis does not summarize results from published studies, as recently done in several other reviews. Rather, we focus on synthesizing *ongoing* studies to tentatively project what studies will likely be completed in the relatively near future.

2. Methods

2.1. Search strategy

A search of the National Institute of Health clinicaltrails.gov database was performed on December 3, 2020. An additional search was conducted on March 13, 2021. The inclusion criteria were interventional or observational clinical studies that investigate psychedelic drugs as treatment to improve symptoms of psychiatric illness. Clinical studies that investigated the mechanistic properties of psychedelic drugs in human participants were also included. An original search of "psychedelics" and "psychiatric disorders" was conducted and cross-referenced with the following terms: MDMA, psilocybin, DMT, 5-MeO-DMT, ibogaine hydrochloride, ayahuasca, LSD and salvia divinorum.

2.2. Study selection and eligibility criteria

A study selection schema can be found in Fig. 1. All completed, active and upcoming clinical studies involving randomized and non-randomized clinical studies were identified and included in the current review. Mechanistic studies that recruited healthy participants and observational studies were also included. In order to gain a

Table 1
Characteristics of trials.

Characteristics	MDMA (n = 32)	Psilocybin (n = 29)	Ayahuasca (n = 1)	Ibogaine hydrochloride (n = 2)	Salvia divinorum (n = 1)	LSD (n = 3)	5-MeO-DMT (n = 1)	DMT Fumarate (n = 1)
Study status								
Active, not recruiting	2 (6.3%)	4 (13.8%)	–	–	–	–	–	–
Completed	23 (71.9%)	3 (10.3%)	1 (100%)	–	–	1 (33.3%)	–	–
Recruiting	4 (12.5%)	14 (48.3%)	–	1 (50%)	1 (100%)	2 (66.7%)	1 (100%)	1 (100%)
Not yet recruiting	2 (6.3%)	8 (27.6%)	–	1 (50%)	–	–	–	–
Temporarily not available	1 (3.1%)	–	–	–	–	–	–	–
Primary Purpose								
Treatment	19 (59.4%)	28 (96.6%)	1 (100%)	2 (100%)	–	3 (100%)	1 (100%)	1 (100%)
Mechanisms of action	10 (31.3%)	–	–	–	–	–	–	–
Prevention	1 (3.1%)	–	–	–	–	–	–	–
N/A	1 (3.1%)	1 (3.4%)	–	–	1 (100%)	–	–	–
Other	1 (3.1%)	–	–	–	–	–	–	–
Allocation								
Randomized	19 (59.4%)	17 (58.6%)	1 (100%)	2 (100%)	–	3 (100%)	–	1 (100%)
Non-Randomized	1 (3.1%)	1 (3.4%)	–	–	–	–	1 (100%)	–
Interventional Model								
Crossover	9 (28.1%)	2 (6.9%)	–	–	–	1 (33.3%)	–	–
Parallel	12 (37.5%)	15 (51.7%)	1 (100%)	1 (50%)	–	2 (66.7%)	–	1 (100%)
Single group	10 (31.3%)	10 (34.4%)	–	–	–	–	–	–
Factorial	–	–	–	1 (50%)	–	–	–	–
Community	–	1 (3.4%)	–	–	–	–	–	–
Sequential	–	–	–	–	–	–	1 (100%)	–
Masking model								
Double	4 (12.5%)	2 (6.9%)	–	–	–	–	–	–
Triple	11 (34.4%)	4 (13.8%)	1 (100%)	–	–	–	–	–
Quadruple	7 (21.9%)	8 (27.6%)	–	2 (100%)	–	3 (100%)	–	1 (100%)
Single	–	1 (3.4%)	–	–	–	–	–	–
None (open label)	9 (28.1%)	12 (41.4%)	–	–	1 (100%)	–	1 (100%)	–
Age group								
Adult (18–65)	18 (56.3%)	18 (62%)	1 (100%)	2 (100%)	1 (100%)	–	1 (100%)	–
Adult and older adult	14 (43.7%)	11 (38%)	–	–	–	3 (100%)	–	1 (100%)
Gender								
Female	1 (3.1%)	2 (6.9%)	–	–	–	–	–	–
Male	–	–	–	–	–	–	–	–
Both	31 (96.9%)	27 (93.1%)	1 (100%)	2 (100%)	1 (100%)	3 (100%)	1 (1005)	1 (100%)
Sponsor								
Academic	31 (96.9%)	27 (93.1%)	1 (100%)	1 (50%)	1 (100%)	3 (100%)	–	–
NIH	1 (3.1%)	–	–	–	–	–	–	–
Corporations	–	2 (6.9%)	–	1 (50%)	–	–	1 (100%)	1 (100%)
Site locations								
Asia	–	–	–	–	1 (100%)	–	–	–
Australia	–	–	–	–	–	–	–	–
Europe	10 (31.2%)	7 (24.1%)	–	1 (50%)	–	3 (100%)	1 (100%)	1 (100%)
Middle East	1 (3.1%)	–	–	–	–	–	–	–
USA	16 (50%)	22 (75.9%)	–	–	–	–	–	–
Canada	2 (6.3%)	–	–	–	–	–	–	–
South America	–	–	1 (100%)	1 (50%)	–	–	–	–
Multicenter	2 (6.3%)	–	–	–	–	–	–	–
Result status								
Has results	4 (12.5%)	2 (6.9%)	–	–	–	–	–	–
No results	28 (87.5%)	27 (93.1%)	1 (100%)	2 (100%)	1 (100%)	3 (100%)	1 (100%)	1 (100%)

comprehensive understanding of all registered clinical studies investigating psychedelic drugs and psychiatric disorders, a brief analysis on suspended, withdrawn or terminated studies was included (Table 6), but excluded from the overall analysis.

2.3. Data extraction and analysis

Data recorded for each clinical study included study type, phase, allocation, intervention model, masking, primary outcome, estimated start and end dates, actual completion duration, method of administration, dose, number of doses, drug type, control condition (if

Table 2
Trial Characteristics stratified by trial phase.

All trials	1	1,2	2	3	N/A
n (%)	19 (27.1%)	5 (7.2%)	37 (53.6%)	2 (2.8%)	7 (10%)
Therapy Type					
MDMA	11 (57.9%)	1 (20%)	15 (40.5%)	2 (100%)	3 (42.8%)
Psilocybin	8 (42.1%)	1 (20%)	17 (45.9%)	–	3 (42.8%)
Ayahuasca	–	1 (20%)	–	–	–
Ibogaine hydrochloride	–	–	2 (5.4%)	–	–
Salvia divinorum	–	–	–	–	1 (14.3%)
LSD	–	–	3 (8.1%)	–	–
5-Meo-DMT	–	1 (20%)	–	–	–
DMT Fumarate	–	1 (20%)	–	–	–
Allocation					
Non-Randomized	1 (5.3%)	1 (20%)	1 (2.7%)	–	–
Randomized	10 (52.6)	2 (40%)	27 (73%)	2 (100%)	2 (28.5%)
Sponsor					
Academic	18 (94.7%)	3 (60%)	35 (94.6%)	2 (100%)	6 (85.8%)
NIH	1 (5.3%)	–	–	–	–
Corporations	–	2 (40%)	2 (5.4%)	–	1 (14.3%)
Study status					
Active, not recruiting	1 (5.3%)	–	5 (13.5%)	–	–
Completed	11 (57.9%)	2 (40%)	12 (32.4%)	1 (50%)	2 (28.6%)
Recruiting	7 (36.8%)	2 (40%)	11 (29.7%)	1 (50%)	2 (28.6%)
Not yet recruiting	–	1 (20%)	9 (24.3%)	–	1 (14.4%)
Psychiatric diagnosis					
MDD	3 (15.8%)	2 (40%)	8 (21.6%)	–	1 (14.3%)
OCD	1 (5.3%)	–	–	–	–
PTSD	1 (5.3%)	1 (20%)	12 (32.4%)	2 (100%)	1 (14.3%)
Substance related disorders	4 (21.1%)	–	1 (2.7%)	–	1 (14.3%)
Alcohol use disorder	1 (5.3%)	–	6 (16.2%)	–	–
Anxiety	2 (10.5%)	–	3 (8.1%)	–	–
Anorexia nervosa	1 (5.3%)	1 (20%)	1 (2.7%)	–	–
Mood disorders	5 (26.3%)	–	–	–	1 (14.3%)
Treatment resistant depression	–	1 (20%)	3 (8.1%)	–	2 (28.5%)
Severe somatic disorder	–	–	1 (2.7%)	–	–
Autism spectrum disorder	1 (5.3%)	–	–	–	–
Drug addiction	–	–	1 (2.7%)	–	1 (14.3%)
Interventional mode					
Oral	13 (68.4%)	2 (40%)	24 (64.9%)	–	5 (71.6%)
Nasal	–	1 (20%)	–	–	–
Intravenous	–	1 (20%)	–	–	–
Not defined	6 (31.6%)	1 (20%)	13 (35.1%)	2 (100%)	2 (28.5%)
Results status					
Has results	2 (10.5%)	–	3 (8.1%)	–	1 (14.2%)
No results	17 (89.5%)	5 (100%)	34 (91.9%)	2 (100%)	6 (85.8%)

AbbreviationsMDD: Major depressive disorder; OCD: Obsessive compulsive disorder; PTSD: Post-traumatic stress disorder; NIH, national institute of health.

applicable), behavioural interventions, location, sponsor, and sample characteristics. After extraction of relevant clinical study parameters, data were analyzed by a descriptive statistical method using IBM SPSS Statistical Software (Version 25). Research methods were adopted from a similar study by Peyrovian et al. (2020), which investigated registered clinical trials of ketamine for psychiatric disorders. The current analysis is also similar to studies typical in the field of oncology, in which high volumes of ongoing clinical trials are common (Barth et al., 2018; Cushman et al., 2018).

3. Results

70 registered clinical studies met the inclusion criteria. Details of studies that met the inclusion criteria are outlined in Tables 1–4. Of the 70 studies, 21 registered studies have published findings, which are outlined in Table 5. The number of studies started each year, number of studies in each phase, number of treatment doses per drug and the varying doses administered of each drug can be seen in Figs. 2–7. An additional four studies were either terminated, suspended or withdrawn (Table 6).

3.1. Characteristics of all studies

At the time of data extraction (December 2020), 32 studies used MDMA, 29 studies used psilocybin, one study used Ayahuasca, three studies used LSD, two studies used ibogaine hydrochloride, one study used salvia divinorum, one study used 5-MeO-DMT and one study used DMT fumarate. Furthermore, 28 studies were completed (40%), six were active and not recruiting (8.5%), 24 were recruiting (34%) and 11 were not yet recruiting (15.7%). In addition to these studies, two studies investigating MDMA were terminated, one study investigating psilocybin was suspended and one was withdrawn (Table 6). These four studies are not included in the remaining analyses. 55 studies (78.5%) were treatment studies, 10 (14.2%) were mechanistic studies and one (1.4%) was a prevention study. The majority of the studies included all genders (95.8%) and three studies (4.2%) included only female participants. 41 studies (58.5%) included adult participants (18–65 years) and 29 studies (41.4%) included any participants aged 18 years and older. Clinical studies focused on a range of psychiatric disorders, including alcohol use disorder (10%), anorexia nervosa (4.2%), anxiety disorders (7.1%), autism spectrum disorder (1.4%), drug addiction (2.8%), MDD (18.5%), mood disorders (8.5%), obsessive compulsive disorder (1.4%), PTSD (24.2%), severe somatic diseases (1.4%), substance related disorders (8.5%) and treatment resistant depression (8.5%). Of the PTSD studies, five (27.8%) only included participants with PTSD due to combat-related activity or being a victim of a serious crime. Inclusion criteria for other PTSD studies were at least moderate PTSD (11.1%), at least moderate PTSD with at least one failed treatment attempt, (22.2%), at least one failed treatment attempt (5.5%), and at least severe PTSD (22.2%). Two studies indicated participants must have a diagnosis of PTSD, determined by the Clinician Administered PTSD Scale, but the severity of PTSD was not specified.

3.2. Characteristics of MDMA studies

Studies investigating the effects of MDMA for psychiatric disorders were most common (45.7%). Of the 32 studies, 23 (71.9%) are completed, two (6.3%) are active but not recruiting, four (12.5%) are recruiting, two are not yet recruiting (6.3%) and one status was not available (3.1%) (Table 1). Amongst all studies, a total of 1014 participants were recruited. The primary purpose of 19 (59.4%) of the studies was treatment, for 10 studies (31.3%) the primary purpose was understanding mechanisms of action and for one study (3.1%) the primary purpose was prevention. 34.3% of MDMA studies are in phase 1, 1.4% are in phase 1 and 2, 46.8% are in phase 2 and 6.2% are in phase 3 (Table 2). The majority of the studies (53.1%) investigated MDMA and

Table 3
Enrollment based on trial characteristics.

Characteristics	Mean number of participants enrolled across all registered trials	Minimum number of participants enrolled in a registered trial	Maximum number of participants enrolled in a registered trial	Total number of participants enrolled across all registered trials
All trials	40.93	1	216	2865
Drug type				
MDMA	31.69	3	187	1014
Psilocybin	54.72	10	216	1587
Ayahuasca	35	35	35	35
Ibogaine hydrochloride	16	12	20	32
Salvia divinorum	1	1	1	1
LSD	37.33	12	60	112
5-MeO-DMT	16	16	16	16
DMT Fumarate	68	68	68	68
Allocation				
Randomized	49.35	6	216	2122
Non-Randomized	21.33	12	36	64
Study status				
Active, not recruiting	55.17	10	180	331
Completed	27.61	3	187	773
Recruiting	52.37	1	216	1257
Not yet recruiting	41.27	10	144	454
Phase				
I	29.42	10	187	559
I/II	30.2	12	68	151
II	41.03	3	216	1518
III	100	100	100	200
Not applicable	62.42	1	150	437
Primary psychiatric condition				
MDD	43.21	1	90	605
OCD	30	30	30	30
PTSD	29.12	3	100	495
Substance related disorders	62	10	187	372
Alcohol use disorder	46	10	180	322
Anxiety	16.6	12	29	83
Anorexia nervosa	23.5	18	36	94
Mood disorders	16	16	16	96
Treatment resistant depression	99.67	12	216	598
Severe somatic disorder	40	40	40	40
Autism spectrum disorder	45	45	45	45
Drug addiction	42.5	20	65	85

AbbreviationsMDD: Major depressive disorder; OCD: Obsessive compulsive disorder; PTSD: Post-traumatic stress disorder.

PTSD, 9.4% focused on substance related disorders, 3.1% focused on alcohol use disorder, 3.1% on drug addiction, 6.3% on anxiety disorders, 3.1% on anorexia nervosa, 18.8% on mood disorders and 3.1% on autism spectrum disorder (Table 4). Half of the MDMA studies included MDMA-assisted psychotherapy, with one study specifying the administration of cognitive behavior therapy (Table 4). A single dose of 125 mg was most common amongst studies, followed by 120–180 mg and three doses.

3.3. Characteristics of psilocybin studies

The majority of the remaining studies (41.4%) investigated treatment using psilocybin. Of the 29 studies registered, three (10.3%) are completed, four (13.8%) are active and not recruiting, 14 (48.3%) are recruiting and eight (27.6%) are not yet recruiting (Table 1). Amongst all studies, a total of 1587 participants will be recruited. The primary purpose of the majority of the studies (96.6%) was treatment. Eight (27.5%) studies are in phase 1, one (3.4%) study is in phases 1 and 2 and 17 (58.6%) studies are in phase 2. 10 (34.5%) studies are investigating psilocybin for MDD, three (10.3%) are examining substance related disorders, five (17.2%) are focused on alcohol use disorder, two (6.9%) are on anxiety disorders, three (10.3%) are on anorexia nervosa and five (17.2%) are on treatment resistant depression (Table 4). Three of the studies examined psilocybin-assisted psychotherapy (Table 4). 69% of studies administered psilocybin orally. A single dose of 25 mg and 0.1–0.3 mg/kg were used most frequently. Out of the 29 psilocybin studies, seven used microdoses, with six studies using doses of 0.1–0.3 mg/kg and one using 1 mg.

3.4. Characteristics of ayahuasca studies

One registered study investigated Ayahuasca for the treatment of MDD. It was a randomized study that took place in South America. A total of 35 participants were enrolled in this study. This study is completed but results are not posted on clinicaltrials.gov. This study protocol included a single dose of oral Ayahuasca.

3.5. Characteristics of ibogaine hydrochloride studies

Two studies are currently registered investigating ibogaine hydrochloride for treatment, one of which recruited participants with alcohol use disorder and the other recruited participants with drug addiction. One of the studies is in the recruiting phase and the other is not yet recruiting. Both are randomized studies, but only one is placebo-controlled. A total of 32 participants are enrolled between the two studies. In one study, participants will receive three doses of ibogaine hydrochloride during the study, at 240 mg, 320 mg, and 400 mg, respectively. In the other study participants will receive six doses of the

Table 4
Clinical Characteristics of trials.

Characteristics	MDMA	Psilocybin	Ayahuasca	Ibogaine hydrochloride	Salvia divinorum	LSD	5-MeO-DMT	DMT Fumarate
Primary Psychiatric Condition								
MDD	–	10 (34.5%)	1 (100%)	–	1 (100%)	1 (33.3%)	–	1 (100%)
OCD	–	1 (3.4%)	–	–	–	–	–	–
PTSD	17 (53.1%)	–	–	–	–	–	–	–
Substance related disorders	3 (9.4%)	3 (10.3%)	–	–	–	–	–	–
Alcohol use disorder	1 (3.1%)	5 (17.2%)	–	1 (50%)	–	–	–	–
Drug addiction	1 (3.1%)	–		1 (50%)			–	–
Anxiety	2 (6.3%)	2 (6.9%)	–	–	–	1 (33.3%)	–	–
Anorexia nervosa	1 (3.1%)	3 (10.3%)	–	–	–		–	–
Mood disorders	6 (18.8%)	–	–	–	–	–	–	–
Treatment resistant depression	–	5 (17.2%)	–	–	–	–	1 (100%)	–
Severe somatic disorders	–	–	–	–	–	1 (33.3%)	–	–
Autism spectrum disorder	1 (3.1%)	–	–	–	–	–	–	–
Additional interventions								
CBT	1 (3.1%)	–	–	–	–	–	–	–
Psychotherapy	16 (50%)	3 (10.3%)	–	–	–	2 (66.7%)	–	–
NRT	–	1 (3.4%)	–	–	–	–	–	–
META	–	1 (3.4%)	–	–	–	–	–	–
Other psychotropic	1 (3.1%)	5 (17%)	–	–	–	–	–	–
Intervention mode								
Oral	19 (59.4%)	20 (69%)	1 (100%)	1 (50%)	–	2 (66.7%)	–	–
Nasal	–	–	–	–	–	–	1 (100%)	–
Intravenous	–	–	–	–	–	–	–	1 (100%)
Not defined	13 (40.6%)	9 (31%)	–	1 (50%)	1 (100%)	1 (33.3%)	–	–
Control condition								
Manitol	2 (6.3%)	2 (6.9%)	–	–	–	1 (33.3%)	–	–
Niacin	1 (3.1%)	5 (17.2%)	–	–	–	–	–	–
Lactose	1 (3.1%)	–	–	–	–	–	–	–
Ketamine	–	1 (3.4%)	–	–	–	–	–	–
Microcrystalline cellulose	–	2 (6.9%)	–	–	–	–	–	–
Nicotinamide	–	1 (3.4%)	–	–	–	–	–	–
None	4 (12.5%)	5 (17.2%)	–	1 (50%)	1 (100%)	–	1 (100%)	–
Not defined	24 (75%)	13 (44.8%)	1 (100%)	1 (50%)	–	2 (66.7%)	–	1 (100%)

AbbreviationsMDD: Major depressive disorder; OCD: Obsessive compulsive disorder; PTSD: Post-traumatic stress disorder; CBT: Cognitive behavioural therapy; NRT: Nicotine Replacement Therapy; META: Motivational Enhancement and Taking Action; RCT: Randomized controlled trial.

study drug. Half of the participants will receive ascending doses (100 mg, 200 mg, 300 mg, 400 mg, 500 mg and 600 mg) and the other half will receive 100 mg each time.

3.6. Characteristics of salvia divinorum studies

One registered study is investigating salvia divinorum for the treatment of MDD. It is in phase 1,2 and is currently recruiting participants. The study is a prospective cohort study with a start date of September 2012. It is an open-label study, with only one participant currently enrolled.

3.7. Characteristics of LSD studies

Three phase 3, randomized clinical studies are registered, one of which is completed and two are in the recruiting phase. All studies were treatment studies. One study is investigating LSD in the treatment of MDD, one is looking at anxiety disorders and one is looking at severe somatic disorders. A total of 112 participants are enrolled amongst the three studies.

3.8. Characteristics of 5-MeO-DMT studies

One registered study is investigating 5-MeO-DMT for treatment resistant depression. It is in phase 1,2 and is currently recruiting participants. The study is interventional, non-randomized with a sequential interventional model and none (open label) masking. The primary purpose is treatment and there are currently 16 participants enrolled.

3.9. Characteristics of DMT fumarate studies

One registered study is investigating intravenous DMT-Fumarate for the treatment of MDD. It is in phase 1,2 and is currently recruiting participants. The study is interventional, randomized with a parallel interventional model and quadruple masking. The primary purpose of the study is treatment with 68 participants enrolled.

4. Discussion

In this systematic review we investigated ongoing studies of psychedelics registered on clinicaltrials.gov. There has been a substantial increase in the number of clinical studies using psychedelics since 2000, with the number of new studies peaking in 2020. The United States of America had the largest number of sites, followed by Switzerland. The majority of studies were in Phase 2. The most common method of administration was oral. Most of the studies were randomized with parallel assignment and quadruple masking. Between 10 and 30 participants were enrolled in the majority of the studies.

MDMA was the most commonly studied psychedelic and PTSD was the most common primary psychiatric disorder for which MDMA's effect was investigated. This may be attributed to the MDMA mechanism of action: monoamine release, serotonin, and norepinephrine transporter

Table 5
Trials with publication.

NCT Number	Psychedelic Drug	Start	Condition	Study design	Phase	Age	Enrollment	Site	Assessments	Protocol
NCT02914769	Ayahuasca	2014	MDD	RCT, TBS, Parallel	1,2	18–60	35	Brazil	MADRS	Patients underwent a wash-out period, between 7 and 14 days prior experimental session and then received single dose oral Ayahuasca
NCT02008396	MDMA	2014	Anxiety in Autistic Adults	RCT, TBS, Parallel	2	21 <	12	USA	LSAS	75–125 mg oral MDMA during two psychotherapy sessions lasting approximately 7 h
NCT01958593	MDMA	2013	PTSD	RCT, TBS, Parallel	2	21 <	6	Canada	CAPS	Three times full dose MDMA + Psychotherapy before and after experimental sessions
NCT01793610	MDMA	2012	PTSD	RCT, TBS, Parallel	2	18 <	29	USA	CAPS	Two active doses of MDMA, active dose 1 (100 mg) and active dose 2 (125 mg), to a comparator dose of MDMA (40 mg) during psychotherapy sessions.
NCT01771874	MDMA	2013	Substance-related Disorders	Non RCT, QTB, Single group	1	18–45	16	Switzerland	Mood Effects	125 mg single dose MDMA
NCT01689740	MDMA	2013	PTSD	RCT, TBS, Parallel	2	18 <	10	Israel	CAPS	125 mg and 25 mg of MDMA + psychotherapy
NCT01386177	MDMA	2011	Mood Disorder + Substance-Related Disorders	RCT, QBS, Single group	1	18–45	16	Switzerland	Systolic and diastolic blood pressure	125 mg single dose MDMA
NCT01270672	MDMA	2011	Mood Disorder + Substance-Related Disorders	RCT, QBS, Cross over	N/A	18–45	16	Switzerland	Systolic and diastolic blood pressure	125 mg single dose MDMA
NCT01211405	MDMA	2010	PTSD	RCT, TBS, Single group	2	18 <	26	USA	CAPS	30 mg, 75 mg and 125 mg of MDMA + Psychotherapy
NCT01148342	MDMA	2004	Substance-related Disorders	RCT, Cross over	1	18–40	187	USA	Human brain function	1.6 mg/kg oral MDMA
NCT01136278	MDMA	2010	Mood Disorder + Substance-Related Disorders	RCT, DBS, Cross over	1	18–45	16	Switzerland	–	125 mg single dose MDMA
NCT00990067	MDMA	2009	Mood Disorder + Substance-Related Disorders	RCT, DBS, Cross over	1	18–45	16	Switzerland	–	125 mg single dose MDMA
NCT00353938	MDMA	2006	PTSD	RCT, TBS, Parallel	2	18 <	14	Switzerland	CAPS	125 mg and 25 mg MDMA + Psychotherapy
NCT00090064	MDMA	2004	PTSD	RCT, TBS, Parallel	2	18–70	23	USA	CAPS	125 mg MDMA followed 2–2.5 h later by 62.5 mg MDMA during course of each of two day-long psychotherapy
NCT01951508	MDMA	2013	Mood Disorder + Substance-Related Disorders	Non RCT, QTB, Cross over	1	18–45	24	Switzerland	Functional magnetic resonance (MR) images measuring BOLD (blood oxygen level dependency)	60 mg single dose MDMA
NCT00886886	MDMA	2009	Mood Disorder + Substance-Related Disorders	RCT, DBS, Cross over	1	18–45	16	Switzerland	–	125 mg single dose MDMA
NCT00957359	Psilocybin	2009	Cancer anxiety	RCT, QBS,	1	18–76	29	USA	HADS	Single dose 0.3 mg/kg oral Psilocybin

(*continued on next page*)

Table 5 (*continued*)

NCT Number	Psychedelic Drug	Start	Condition	Study design	Phase	Age	Enrollment	Site	Assessments	Protocol
NCT00302744	Psilocybin	2004	Cancer anxiety	Cross over NCT, QBS, single group	1	18–70	12	USA	–	Single dose 0.2 mg/kg oral Psilocybin
NCT02950467	Psilocybin	2018	MDD	CT, None, Single group	1	50 <	30	USA	–	Single dose oral Psilocybin
NCT02427568	MDMA	2015	Anxiety	RCT, QBS, Parallel	2	18 <	18	USA	STAI	125 mg MDMA administered 2–4 weeks apart followed 1.25–2.5 h later by a supplemental dose of 62.5 mg MDMA.
NCT00920387	LSD	2008	Anxiety	RCT, QBS, Parallel	2	18 <	12	Switzerland	STAI	200 mcg LSD once during each of two LSD-assisted psychotherapy sessions scheduled two to four weeks apart

AbbreviationsMADRS: Montgomery–Åsberg Depression Rating Scale; CAPS: Clinician Administered post-traumatic stress disorder Scale; STAI: State-Trait Anxiety Inventory; HADS: Hospital Anxiety and Depression Scale; RCT: Randomized clinical trial. DBS: Double blind study. MDD: major depressive disorder; PTSD: post-traumatic stress disorder; QBS: Quadruple blind study; RCT: randomized clinical trial; TBS: triple blind study.

Table 6
Characteristics of suspended, terminated and withdrawn studies.

Characteristics	Suspended	Terminated	Withdrawn
Therapy type			
MDMA	–	2 (100%)	–
Psilocybin	1 (100%)	–	1 (100%)
Primary psychiatric condition			
OCD	1 (100%)	–	–
PTSD	–	1 (50%)	–
Anxiety	–	1 (50%)	1 (100%)
Primary purpose			
Treatment	1 (100%)	2 (100%)	1 (100%)
Intervention mode			
Oral	–	2 (100%)	1 (100%)
Not defined	1 (100%)	–	–
Phase			
1	1 (100%)	–	–
1,2	–	–	–
2	–	2 (100%)	1 (100%)
3	–	–	–
Age group			
Adult (18–65)	1 (100%)	–	–
Adult and older adult	–	2 (100%)	1 (100%)
Site location			
USA	1 (100%)	1 (50%)	1 (100%)
Middle east	–	1 (50%)	–
Total number of enrolled participants	15	14	0

Abbreviations: OCD: Obsessive compulsive disorder; PTSD: Post-traumatic stress disorder.

reuptake inhibition, monoamine oxidase inhibition, partial agonist of serotonin receptors (5-HT2A, 5-HT1A, and 5-HT2C receptors), and increase in blood concentrations of oxytocin (Dumont et al., 2009). MDMA's psychopharmacological characteristics make it potentially well suited as an adjunct to trauma-focused psychotherapy.

Psilocybin was the second most used psychedelic drug in registered studies, and most of the focus was on MDD. The combination of the serotonergic and glutamatergic function of psilocybin and the preliminary evidence of the antidepressant impact of psilocybin-assisted therapy suggest the potential of psilocybin-assisted therapy as a novel antidepressant intervention (Goldberg et al., 2020). These findings are also reflected in review papers which summarize the emerging role of both psilocybin and MDMA in the treatment of psychiatric disorders (Gill et al., 2020). Two registered studies investigated the effects of ibogaine hydrochloride on drug addiction and alcohol use disorder, which is due to ibogaines ability to interrupt addiction to opiates and other substances of abuse (Alper, 2001). Ayahuasca, salvia divinorum, 5-MeO-DMT and DMT fumarate were the least common in studies, with only one study investigating the efficacy of each psychedelic. All four psychedelics were used for the treatment of either MDD or treatment-resistant depression. The emphasis on psychedelics for MDD is also seen in the analysis conducted by Peyrovian et al. (2020), such that the most common psychiatric diagnoses in registered studies using ketamine and esketamine is major depressive episodes, with a specific focus on MDD and treatment-resistant depression. There was a larger number of registered studies investigating ketamine (n = 119) for psychiatric disorders than are currently registered for all other psychedelics combined, as identified in the current analyis (n = 70).

A limitation to the current study is that it was restricted to clinical studies registered on clinicaltrials.gov. There are likely psychedelic studies that are not registered, despite international guidelines encouraging study registration. Moreover, some registered studies were missing information, such as the route of administration and number of doses. As such, this information was missing from the current analysis. It would be useful for investigators to include this information in future protocols. More details regarding the adjunct psychotherapy being used would also be favourable.

Upon examining the current registered studies, gaps in the current research emerged. An area that would be beneficial for future research to address is which type of psychotherapy intervention is most effective in conjunction with the administration of psychedelics. It would also be beneficial for studies to compare the number of doses being administered, in order to determine the most effective range of doses for each drug. Nevertheless, results from the current review indicate that there is an extensive number of ongoing studies investigating the effects of psychedelic drugs for psychiatric disorders. Thus, we recommend that researchers, granting agencies and expert reviewers consider all ongoing, registered projects before initiating novel studies, especially if hoping to investigate MDMA and psilocybin.

Conflict of interest disclosures

RSM discloses speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health,

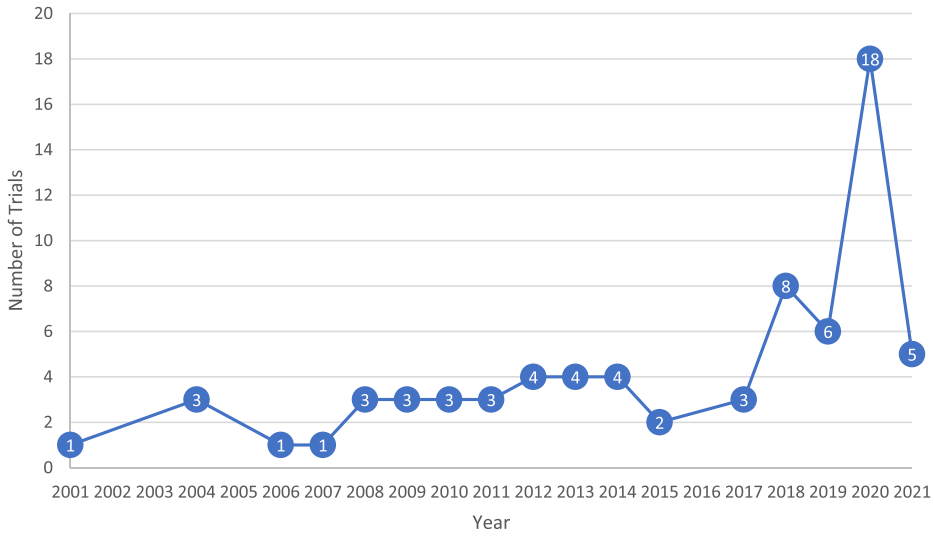

Fig. 2. Number of trials started each year.

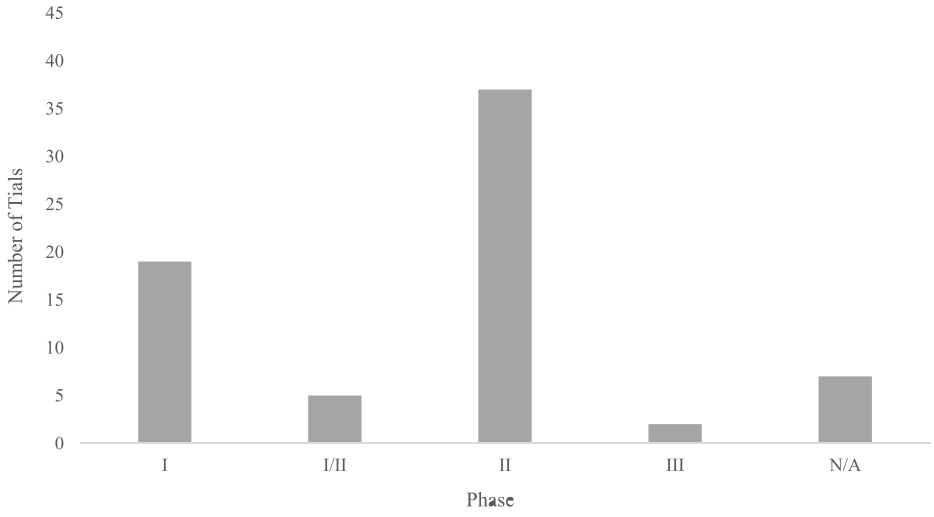

Fig. 3. Number of trials in each phase.

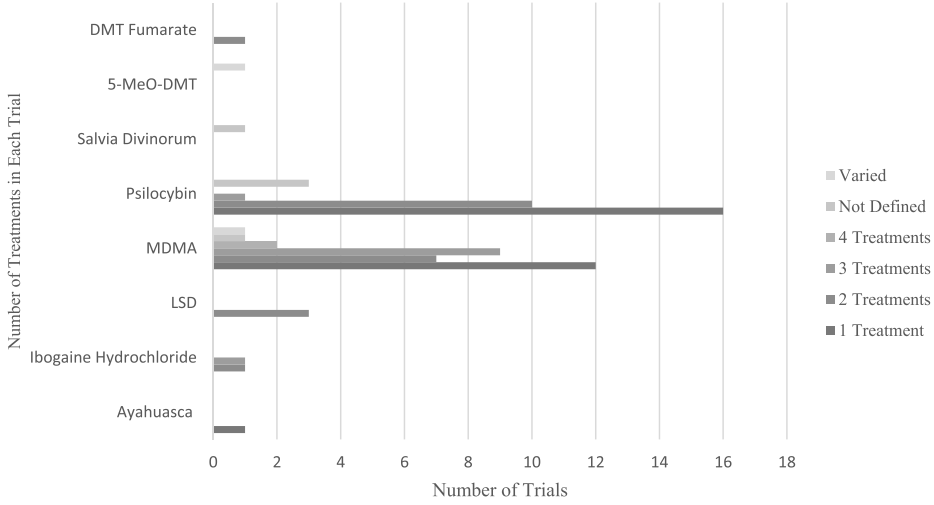

Fig. 4. Number of doses given throughout the duration of trials
Note: Varied indicates that groups of participants received differing number of doses.

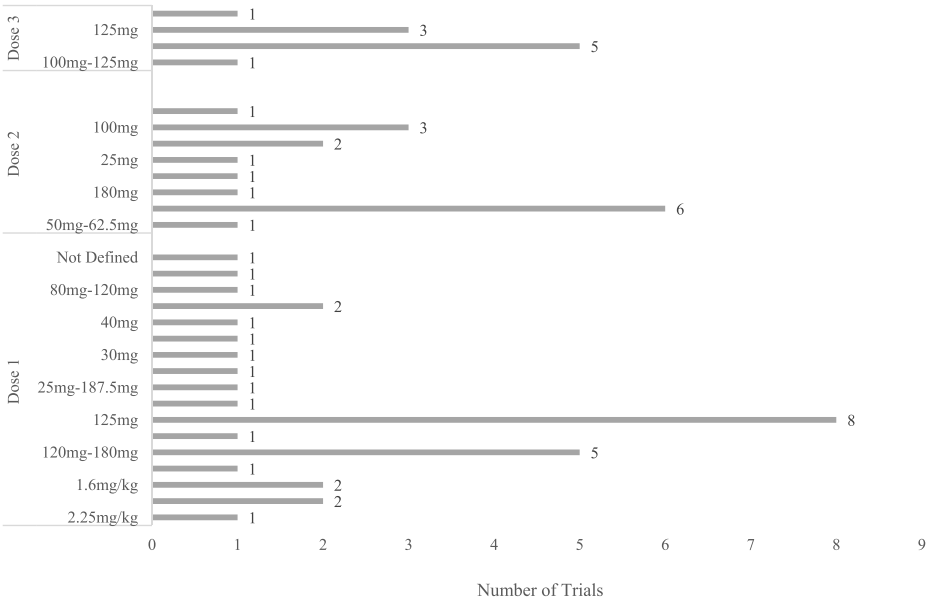

Fig. 5. Doses in MDMA trials.

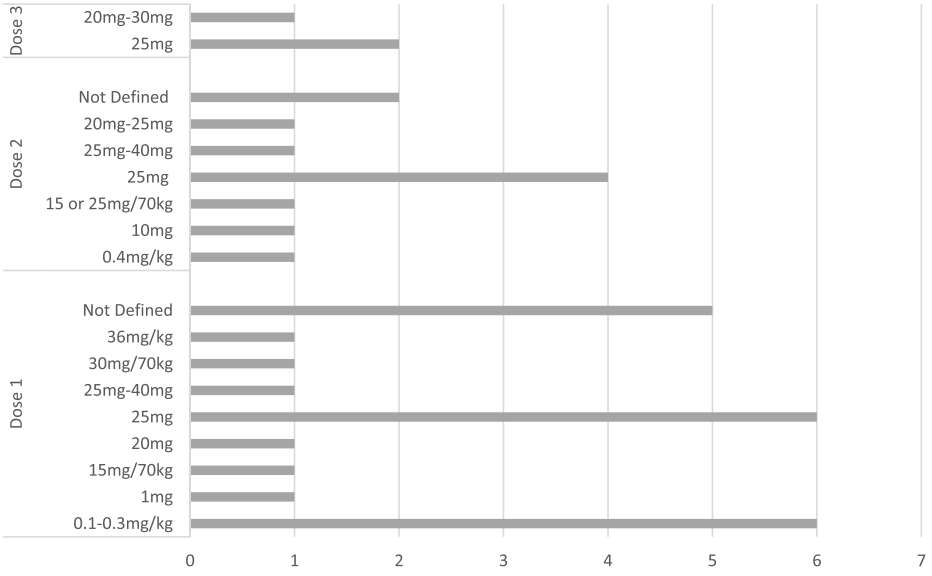

Fig. 6. Doses in psilocybin trials.

Novo Nordisk, Kris, Sanofi, Eisai ,Intra-Cellular, NewBridge Pharmaceuticals, Abbvie. RSM is the CEO of Braxia Scientific Corp. JDR discloses that he has been on advisory boards and/or received honoraria for educational activities and/or research grants from Allergan, Janssen, Lundbeck and COMPASS and is the Medical Director of Braxia Health. All other authors have no conflicts of interest to declare.

Author statement

Ashley Siegel, Shakila Meskat and Katie Benitah were primarily involved in the writing, analysis and synthesis of this review. Joshua Rosenblat conceived the research question and protocol and provided supervision and direction to Ashley Siegel, Shakila Meskat and Katie Benitah. All other authors contributed significantly to the discussion and revision of this work, including analysis, interpretation of results, proofreading, edits and approval for submission.

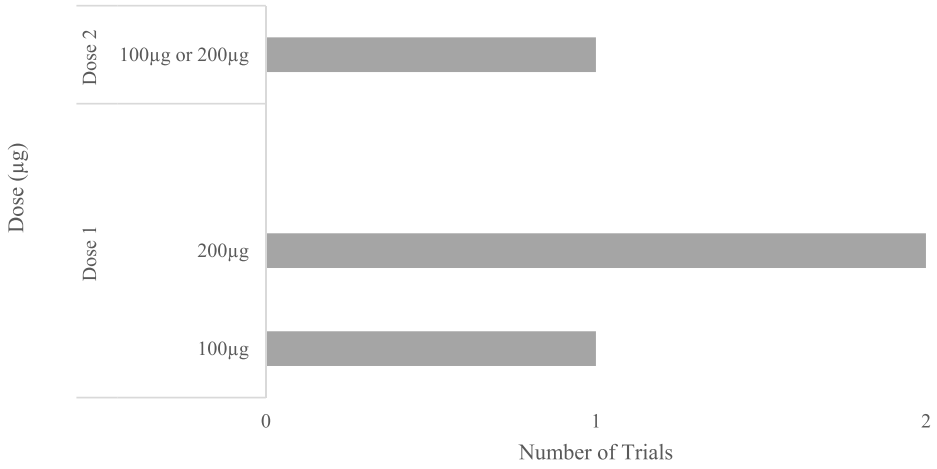

Fig. 7. Doses in LSD trials.

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