HALLUCINOGENS AND ENTACTOGENS: ESTABLISHING A NEW CLASS OF PSYCHOTHERAPEUTIC DRUGS?

EDITED BY: Stefan Borgwardt, Matthew W. Johnson and Felix Müller
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Topic Editors:
Stefan Borgwardt, University of Basel, Switzerland
Matthew W. Johnson, Johns Hopkins University, United States
Felix Müller, University Psychiatric Clinic Basel, Switzerland

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EDITORIAL
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Editorial: Hallucinogens and Entactogens: Establishing a New Class of *Psychotherapeutic* Drugs?

Felix Müller[1]*, *Matthew W. Johnson*[2] *and Stefan Borgwardt*[1,3]

[1] Department of Psychiatry, University of Basel, Basel, Switzerland, [2] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, United States, [3] Department of Psychiatry and Psychotherapy, Translational Psychiatry Unit, University of Lübeck, Lübeck, Germany

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Editorial on the Research Topic

Hallucinogens and Entactogens: Establishing a New Class of Psychotherapeutic Drugs?

The last years have seen an increasing interest in research on hallucinogenic drugs, like psilocybin and LSD. Similar developments were observed for the entactogen MDMA. During the 1950s and 1960s, this field was in the focus, and relatively broad investigations of psilocybin and LSD were conducted, both in basic and clinical research. In this era, psychiatry placed high hopes on these compounds, especially as possible treatment options for various mental diseases. Indeed, many promising observations were made. However, this development came to a halt 50 years ago, when hallucinogens were classified as schedule I drugs. Now, research continues, and the current efforts have been extensive. It seems that we are truly experiencing a revival of the classic hallucinogens psilocybin and LSD. Furthermore, related substances like ibogaine and ayahuasca are investigated systematically for the first time, and this is also true for the therapeutic use of MDMA. Previous findings suggest that a few administrations of these substances might improve symptoms of certain psychiatric disorders in an enduring way, outlasting the acute pharmacological effects by far. It is often assumed that the underlying mechanisms are similar to those which are effective in psychotherapy. This mechanism of action would be unique in psychopharmacology, constituting a new class of *psychotherapeutic* drugs.

Especially, the potential therapeutic applications have become the focus of attention in the public and the scientific community. Although psychiatry has progressed greatly during the 20th century, there are still patients who do not respond well to established interventions and are, therefore, considered treatment-resistant. Moreover, psychopharmacological treatments are often accompanied by side effects, posing a challenge for compliance. Genuine innovations have been rare in psychiatry during the last decades. The path from bench to bedside is difficult, and new approaches often fail to show clinical efficacy. In comparison, there is already considerable experience with hallucinogenic and entactogenic substances, and previous findings are promising. However, research in this field is still in its infancy, and many questions remain open. For example, it still remains to be resolved if previous, encouraging results can be replicated, which patients might benefit from these treatments and which might not, how therapeutic effects can be promoted and risks further minimized.

Some of these questions are investigated by studies of this issue. Three articles rise the fundamental question of mechanism behind therapeutic effects of hallucinogenic and

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Roberto Ciccocioppo, University of Camerino, Italy

***Correspondence:**
Felix Müller
felix.mueller@upkbs.ch

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entactogenic drugs. Heuschkel and Kuypers compare psychological and biological effects of mindfulness practices and the hallucinogen psilocybin. They conclude that a combination of both approaches might show synergistic effects in the treatment of mental diseases like depression. Wolff et al. are aiming to understand therapeutic mechanism of hallucinogens within a cognitive-behavioral framework. They suggest that relaxation of beliefs induced by these drugs open the opportunity for avoidance-free exposure. Preller and Vollenweider review influences of hallucinogens and entactogens on social processing. It is pointed out that LSD and psilocybin induce similar alterations in social processing as MDMA. Compared to these drugs, somewhat different social processing effects were found for GHB, a drug sometimes labelled as an "entactogen" despite a different pharmacology than MDMA. Potential therapeutic implications for different diseases, like depression, anxiety, and addiction, are discussed.

This topic also covers papers on the clinical applications of MDMA and LSD. Fedducia et al. report on their advanced research program on MDMA as a treatment for posttraumatic stress disorder (PTSD). They also compare this approach with already established psychiatric medications. Sessa et al. review the history, pharmacology, and clinical application of MDMA. They also discuss other potential applications of this substance beside PTSD. Basic pharmacological aspects of MDMA are investigated by Vizeli and Liechti. The authors explore the effects of gene variants of the dopamine on the effects of MDMA in humans.

Sexton et al. look at the question whether naturalistic use of different classes of novel and classic hallucinogenic drugs are associated with different psychological symptoms which might inform the debate on differential risk profiles and therapeutic efficacy of these substances. Another naturalistic study conducted by Garcia-Romeu et al. investigates potential positive effects of hallucinogens on misuse of cannabis, opioids, and psychostimulants. Fuentes et al. look at the long history of clinical application of LSD and systemically assess randomized controlled trials with regard to safety and efficacy in several mental diseases. Hutten et al. turn toward the new topic of "microdosing." This study investigates self-reports on the effects of small doses of hallucinogens on mental and somatic symptoms which might inform future studies.

Overall, this issue covers a broad spectrum of questions relevant for clinical research and application of hallucinogens and entactogens. We hope that this collection contributes to the great progress this field has seen in recent years.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this article.

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REVIEW
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A Review of 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy

Ben Sessa, Laurie Higbed and David Nutt*

Neuropsychopharmacology Unit, Department of Medicine, Imperial College London, London, United Kingdom

This paper provides a brief review of the history, proposed pharmacological mechanisms, safety issues, and clinical applications of the medicine 3,4-methylenedioxymethamphetamine (MDMA). Most clinical MDMA research in patients to date has focused on MDMA-assisted psychotherapy to treat posttraumatic stress disorder (PTSD). In this review paper other potential therapeutic applications for MDMA therapy are described, including contemporary studies treating anxiety associated with autism and the authors' ongoing study exploring the potential role for MDMA-assisted psychotherapy to treat alcohol use disorder. MDMA therapy for PTSD is now entering the final Phase 3 stage of drug development, with a target set for licensing by the FDA and EMA in 2021. This means that if clinical efficacy criteria are achieved, MDMA would become a medicine.

Keywords: MDMA (3, 4-methylenedioxymethamphetamine), trauma, addiction, psychotherapy, alcohol

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Edited by:
Stefan Borgwardt,
Universität Basel, Switzerland

Reviewed by:
Michael Crofton Mithoefer,
Medical University of South Carolina, United States
Oscar Prospéro-García,
National Autonomous University of Mexico, Mexico

****Correspondence:***
Ben Sessa
bensessa@gmail.com

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THE EARLY THERAPEUTIC USE OF MDMA

In the late 1960's, after lysergic acid diethylamide (LSD) was banned, some psychedelic therapists began exploring other drugs as tools to enhance psychotherapy. One, Leo Zeff, was initially introduced to MDMA in 1976 by psychedelic chemist, Alexander "Sasha" Shulgin, who had been studying psychedelics since the early 1960s (1). Zeff went on to successfully and safely give MDMA, then legal, to many thousands of patients (2). Shulgin, alongside chemist David E. Nichols, published the first report into the effects and pharmacology of MDMA in humans (3).

Not a "classic" psychedelic drug, but an "entactogen" (4), MDMA produces a more gentle and easily tolerated state compared to LSD. It is shorter-acting, which makes it more clinically manageable, it enhances feelings of empathy and bonding and allows users to access and process memories of emotional trauma (5).

Psychotherapists using MDMA in the early 1980s, when was called "Adam" or "Empathy," wished to keep it within the clinical research community. But MDMA became rebranded as the more marketable "Ecstasy" and its non-clinical use spread—especially in the club scene or in large parties called raves. In 1984, in response to rising police seizures of the drug, the DEA announced that it intended to ban the compound. The clinical MDMA research community requested a hearing to debate the DEA's intention, but in May 1985 MDMA was initially placed in an emergency Schedule One category and subsequently became permanently scheduled thereafter, where it has stayed ever since—hugely restricting opportunities for its research (6). Due to this *Catch 22* situation, very little clinical research was able to take place. This prompted the formation of the US-based research organization, *The Multidisciplinary Association for Psychedelic Studies* (MAPS), which today is spearheading global clinical research of MDMA.

In the mid-eighties, a series of uncontrolled case studies, conducted before the ban, were published. These described the effective use of MDMA with individuals, couples and groups (7, 8). In 1988 the *Swiss Medical Society for Psycholytic Therapy* conducted individual and group psychotherapy with MDMA and LSD. Over a 100 patients with a wide range of psychiatric problems received an average of eight therapeutic sessions. Over 90% of patients described improvements at 19-months follow-up (9). But in 1993 the Swiss Ministry of Health withdrew permission to continue prescribing MDMA and LSD from the Swiss psychiatrists in the wake of concerns about the lack of research methodology and secondary to an ibogaine-related death of a patient (10). The compassionate use of MDMA has restarted in Switzerland in the last years and currently a few patients are treated each year based on individual authorizations by the Federal Office of Public Health.

Throughout the 1990s, tensions developed between the clinical MDMA community, who proposed MDMA was safe in controlled circumstances, and the media and politicians who favored strict prohibition to control recreational use. During this decade the UK brewing industry sponsored widely publicized anti-Ecstasy campaigns in response to their business being eroded by Ecstasy use (11). Undeterred by the political challenges, MDMA clinical research continued, with a MAPS-sponsored clinical study gaining approval in 2000 to look at MDMA for PTSD in Spain. But after just 1 year, a political backlash by the Spanish government shut down the study.

CONTEMPORARY CLINICAL RESEARCH WITH MDMA

The first controlled clinical study demonstrating MDMA-assisted psychotherapy was eventually published in 2010—with impressive results (12). Twenty patients with treatment-resistant PTSD received, during a course of non-drug psychotherapy, either inactive placebo or two or three sessions of MDMA (initial dose of 125 mg, followed 2 h later by a further booster of 62.5 mg). At two and 12-month follow-up, 83% of the experimental group no longer met the criteria for PTSD, compared with just 25% of the patients in the placebo group. There were no drug-related serious adverse events and no adverse neurocognitive effects (12). Long-term follow-up of the cohort of successfully-treated patients demonstrated that remission from PTSD was maintained for up to 6 years (17 to 74 months, mean of 45 months), without having any further doses of MDMA (13).

A second, smaller MAPS-sponsored study in 2013 again explored the potential for MDMA Psychotherapy for treatment-resistant PTSD and showed substantial improvements (14). This study by Oehen was smaller than Mithoefer's and although there was a definite trend in the direction of MDMA therapy being superior to placebo, at first sight the statistics failed to demonstrate a significant reduction in CAPS for the experimental subjects (14). However, a further review of the data, using effect size as a measure, concluded that Oehen had been overly conservative and the results were indicative of MDMA psychotherapy providing substantial improvements for treatment-resistant PTSD (15).

Further teams in the USA, Israel and Canada then began conducting Phase 2 MDMA trials for PTSD. In 2018 a team based in Boulder, Colorado, USA submitted their results of a dose response model from multiple therapy teams on 28 participants (16). Two active doses (100 and 125 mg) were compared with a low dose (40 mg) session, and later the low dose group crossed over for three open-label active dose sessions. The active groups had the largest reduction in CAPS scores at the primary endpoint. The results at the primary endpoint were not significant, but at the 12 month follow-up the difference from baseline did reach significance. There were no drug-related serious adverse events and the treatment was well-tolerated. A further study demonstrated successful treatment of veterans and first responders with treatment-resistant PTSD (17). All of the contemporary MDMA-assisted psychotherapy studies to date have only been carried out on relatively small numbers of patients. Despite the consistently positive results and good tolerability of the treatments described in these studies above, larger, multisite trials are necessary to demonstrate the level of clinical efficacy and safety required to see MDMA become a licensed medicine. This phase of clinical MDMA research is now underway.

In collaboration with the Food and Drugs Administration (FDA) in America and the European Medicines Agency (EMA) in Europe, the pooled data from all of the MAPS-sponsored Phase 2 trials formed the basis for expansion into multi-site Phase 3 trials of MDMA therapy for PTSD, with FDA-granting Breakthrough Therapy designation. Study centers for the MAPS phase 3 programme in the USA are now underway. The European sites—in the UK, Netherlands, Germany and the Czech Republic—are in the process of seeking approvals and are projected to start later in 2019, putting MDMA on course to becoming a licensed treatment in 2021 (18).

THE SAFETY OF CLINICAL MDMA

In the early 2000s—at the height of Ecstasy's demonization in the media—a debate around safety dominated the scientific and popular literature. But comparing clinical MDMA use with recreational ecstasy carries no scientific validity. Clinical subjects are screened, monitored throughout, are given pure drug and are closely followed-up for months afterwards. In contrast recreational ecstasy use frequently involves impure samples of MDMA, taking multiple other drugs and often paying little attention to the physiological aspects of the drug experience. Nevertheless, even when one *does* look at recreational ecstasy, which is used by around 750,000 people every weekend in the UK (19), the rates of morbidity and mortality are low. One study demonstrated that after removing confounding factors of concomitant drugs, there were only three deaths per year attributed solely to MDMA (20). Further studies that control for confounding factors show no evidence of neurotoxicity with MDMA when used in isolation (21) and no lasting neurocognitive impairments (22). Given that Ecstasy has such

widespread use—second only to cannabis in popularity as an illicit drug—these epidemiological and experimental data demonstrate its relative safety.

Despite the absence of evidence for chronic adverse effects from clinical MDMA therapy, acutely the MDMA experience may be associated with transient neurocognitive effects, including verbal and spatial memory deficits, slow processing speeds and executive functioning impairments (23). But these resolve after the acute subjective psychological effects of the drug have worn off (24). Over 1,600 doses of clinical MDMA have being administered in research settings in recent years, with only one report of a drug-related self-limiting serious adverse event and no deaths (18). A large analysis on 166 subjects given MDMA in a controlled setting by Vizeli et al. (25), demonstrated no serious adverse events and showed that MDMA "produced predominantly acute positive subjective drug effects." The analysis also showed that subjective negative drug effects and other adverse effects were significantly more common in women. The paper concluded that, "MDMA administration was overall safe in physically and psychiatrically healthy subjects and in a medical setting."

Compared to other stimulants (particularly cocaine, amphetamine and methamphetamine) addiction to MDMA is very rare. And in the last 15 years of clinical studies with medical MDMA, illicit use of ecstasy after having used it clinically is seldom observed (13).

Clinical MDMA administration typically causes increased blood pressure and heart rate, increased body temperature (25–27), jaw tightness, bruxism, reduced appetite, poor concentration, and impaired balance (12). More serious adverse effects have not been observed in the last 15 years of monitored sessions with clinical MDMA (28). Similarly, the low mood, irritability and fatigue described by Ecstasy users (and dubbed the "mid-week blues") is rarely observed in the clinical setting (13, 29), though low mood has also been reported in healthy subjects after administration of MDMA in controlled settings (30–32). Studies suggest these "blues" are related to recreational users missing sleep, dancing excessively, using other drugs (including alcohol), and going without food (33, 34)—none of which occur in a clinical setting.

MECHANISM OF ACTION OF CLINICAL MDMA

Multiple receptors, neurotransmitters and intermediary processes probably account for MDMA's effects. MDMA mainly acts as a releaser of serotonin (5-HT) and noradrenaline, and to a lesser extent also of dopamine (35, 36). Typical effects of MDMA can be predominantly attributed to the activation of the 5-HT system (31, 37, 38).

Activity at 5-HT_{1A} and 5-HT_{1B} receptors attenuates feelings of depression and anxiety, reduces the amygdala fear response and increases levels of self-confidence (39). Increased feelings of closeness, greater compassion and increased empathy for oneself and others further contribute to positive mood (40, 41). Increased dopamine and noradrenaline raise levels of arousal and awareness (42, 43), motivating engagement in therapy and promoting fear extinction (44).

MDMA's effects at alpha-2 receptors, which contribute to the drug's effects on thermoregulation (45), may also contribute a paradoxical relaxation/sedation effect (46), which could be beneficial in the context of trauma-induced hypervigilance. While adrenergic alpha-1 receptors are involved in the thermogenic response to MDMA in humans (41), alpha-2 receptors do not appear to be critically involved in the psychological effects of MDMA in humans (47).

MDMA has been shown to facilitate the release of oxytocin, the hormone associated with early infantile bonding, which may increase levels of empathy and closeness (48–52) and dampen fear-related amygdala activity, causing a decrease in stress response and social anxiety (53, 54).

Animal studies have demonstrated MDMA increases fear extinction through a mechanism dependent on elevated levels of brain derived neurotropic factor (BDNF) in the amygdala (55, 56), which might account for the observed phenomenon of MDMA psychotherapy allowing for patients' safe recall of painful emotional memories, that are usually avoided due to the overwhelming negative affect that usually accompanies recall of such events. Increased prosocial feelings (57), improved tolerance for unpleasant memories (58) and enhanced empathy and self-compassion (59), can promote a strong therapeutic alliance to effectively process traumatic memories.

In summary, the combined pharmacological effects of MDMA and the associated subjective psychological experience provide a unique selective impairment of the fear response whilst leaving the other faculties intact. Therefore, MDMA could be "the perfect drug for trauma-related psychotherapy" (60).

HOW WE CARRY OUT MDMA-ASSISTED PSYCHOTHERAPY

Psychotherapy with MDMA borrows much of its methodology from the earliest research with LSD in the 1950s. The concept of set and setting is central to the totality of the user's experience; where set refers to the user's mindset and setting refers to the environment in which the drug is taken. Much effort goes into developing the optimum psycho-environmental conditions for a clinical MDMA-assisted session (61). A comprehensive study with a 125 mg MDMA dose taken by 166 subjects in a clinical environment, showed 64% of the subjects gave reports that the they found the controlled setting reassuring and it made them feel safe (25).

Therapeutic sessions with MDMA are typically delivered by a male-female co-therapist dyadic pair. However, a recently completed study of MDMA-assisted Psychotherapy combined with Cognitive Behavioral Combined Therapy for couples in which one person had PTSD, used some co-therapy teams with two female therapists (https://clinicaltrials.gov/ct2/show/NCT02876172). The drug-assisted sessions are non-directive; encouraging the patient to go with the experience. The medicine seems to catalyze the patient's innate healing ability, which does the work (7, 62). The therapists create

a sense of safety and communicate trust in their patient's ability to explore their issues. Eyeshades are frequently employed in MDMA-assisted sessions and the use of music played through headphones is commonplace. Physiological observations such as regular measurements of blood pressure and temperature are also commonplace throughout the MDMA experience.

As well as the MDMA-assisted sessions, the non-drug therapeutic sessions that make up a total course of MDMA psychotherapy are essential for preparation before taking the drug and subsequent integration of the emergent material after the drug sessions. Taken on its own, without adequate pre-drug preparation or post-drug support, MDMA is less likely to have a positive beneficial effect [Mithoefer M—Personal Communication: 'Our observation in Phase 2 clinical trials is that the preparation and follow-up visits are often crucial because the nature of this therapeutic process is that symptoms can increase afterMDMAassisted sessions (as they can in any deep processing of trauma), and without proper support this could lead to deterioration and risk of suicide for a subset of people.With proper support these challenges are ultimately useful and part of the healing trajectory rather than an adverse outcome' (2018)]. In training MDMA Therapists for the future, MAPS are currently leading the way with their manualised approach for MDMA-assisted psychotherapy for PTSD.

FUTURE DIRECTIONS: BROADENING MDMA BEYOND PTSD

Up till now most MDMA therapy research has been conducted with patients with PTSD. But many people suffering with other chronic mental disorders will describe some degree of pre-morbid trauma, often secondary to sexual or physical child abuse, or more commonly emotional abuse and neglect, which are no less damaging to a person's subsequent development (63). Given that such child maltreatment is particularly prevalent in cases of adult addictions (64), we are now exploring the potential role for MDMA therapy in cases of adult alcohol use disorder.

Alcohol use disorder represents a serious clinical, social and personal burden on its sufferers and a significant financial strain on society. Current treatments, both psychological and pharmacological, are poor, with high rates of relapse after medical detoxification and dedicated treatment programs. The earliest historical roots of psychedelic drug-assisted psychotherapy in the 1950s for alcoholism were associated with LSD-assisted psychotherapy (65). Indeed, Bill Wilson, the founder of *Alcoholics Anonymous*, testified to the powerful potential of psychedelic-assisted therapies for treating alcoholism (66). And contemporary pilot studies with psilocybin therapy for alcohol addiction (67) and psilocybin therapy for nicotine addiction (68) have demonstrated positive results. But MDMA-assisted psychotherapy has never been explored as a treatment for any form of substance use disorder. However, MDMA could be well suited to allow a patient using alcohol as a form of self-medication against a history of childhood trauma to explore and address painful memories without being overwhelmed by negative affect. Furthermore, the acute psychological effects of MDMA, which are typically less perceptually disturbing than those produced by classic psychedelics, may be more easily tolerated by some people. Given that compliance is a critical part of addiction therapy, there are good grounds for exploring MDMA therapy for alcoholism (69). However, it must be borne in mind that the cardiovascular tolerability of MDMA is lower compared with hallucinogens (25, 50), which prompts the requirement for more robust vital signs monitoring during MDMA therapy compared to classic psychedelic drug-assisted psychotherapy.

The capacity for MDMA to increase feelings of empathy and compassion for the self and others may contribute to improved self-awareness and subsequently reduce the denial of alcohol misuse (70). Similarly, MDMA has been shown to increase feelings of mindfulness, which has been increasingly explored as a potential approach for treating alcohol use disorder (71). This is the hypothesis behind the UK's first ever clinical MDMA Therapy study, the Bristol-Imperial MDMA-for-Alcoholism (BIMA) study (69). The BIMA study enrols participants into an 8-week course of supportive psychotherapy employing elements of Motivational Interviewing. As with all psychedelic-drug assisted psychotherapy courses, most of therapeutic sessions are face-to-face *non*-drug-assisted sessions. Only on two occasions participants are administered open-label sessions of MDMA-assisted therapy. On each drug-assisted session participants receive an initial dose of 125 mg MDMA, followed 2 h later by a "booster dose" of 62.5 mg to prolong the experience. Throughout the drug-assisted session, vital signs, including blood pressure and body temperature, are monitored. Participants remain in the treatment center overnight after taking MDMA. Mood, sleep and suicide risk are monitored daily for a week. Participants are followed-up for 9-months post-detox, and outcome measures include safety and tolerability data, quality of life measures, physical and mental health status and drinking behaviors (69). This study will be completed by the end of 2019.

Another area of contemporary research with MDMA therapy has explored the potential for relief of social anxiety associated with autism, in a MAPS-sponsored randomized, double-blind, placebo-controlled pilot study completed at Harbor-UCLA Medical Center and Stanford University (72). One of the cardinal features of autism is a tendency for a sufferer to lack empathy. It is a recognized anecdotal observation that autistic adults often report reduced empathy-impairments during, and for some time after, taking MDMA (72).

Other contemporary areas of research with MDMA therapy include the potential for MDMA-assisted psychotherapy in treating mood disorders (73) and, relatedly, as an alternative to electro-convulsive therapy (74).

SUMMARY AND CONCLUSION

As MAPS pushes ahead with Phase 3 studies in the USA and Europe for MDMA therapy for PTSD, we are seeing a broadening of the clinical possibilities for the compound. Meanwhile psychiatrists are increasingly recognizing the role

played by early psychological trauma in a range of mental disorders beyond that of PTSD (69).

Due to its association with recreational Ecstasy, MDMA has a long-standing label of controversy in the UK. But this narrative must be tackled; partly because the compound is demonstrably safe and efficacious in the clinical setting and partly because politics and erroneous media-driven opinion must not be allowed to dictate the progress of medical research (75). Like everything else, MDMA is not 100% safe. As with all medical interventions—from sticking plasters to cancer chemotherapy—MDMA may be simultaneously both invasive and beneficial and therefore the same principles of evidence-based clinical governance must be applied to psychedelics as they are to other therapeutic approaches (76). Clinical MDMA and recreational ecstasy are incomparable in terms of drug purity, administration and the screening and monitoring of selected participants. "Prohibition of MDMA and other illicit drugs increases, not reduces, the potential harms of recreational drug use (75), adds unnecessary costs that put research beyond the financial capabilities of many academic institutions, and therefore hold back progress (77)."

There remains much work to be done to convince critics that a compound that is experienced recreationally by so many people may also, in its clinical form, have benefits for patients suffering with treatment-resistant mental disorders. Meanwhile, psychedelic culture is enjoying a palpable renaissance in both medicine and the media. Against this backdrop, psychiatry and society continue to be burdened with far-from-perfect treatment outcomes for many mental disorders. In this context, given the clinical burden, the lack of treatment efficacy and their continued distress, perhaps the only question we should be asking is: Can we afford *not* to explore MDMA therapy for our worthy patients?

AUTHOR CONTRIBUTIONS

BS wrote the main body of the paper, including citations. LH and DN added further commentary and reviewed and edited the paper.

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REVIEW
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Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline

Allison A. Feduccia[1], Lisa Jerome[1], Berra Yazar-Klosinski[2], Amy Emerson[3], Michael C. Mithoefer[4] and Rick Doblin[2]*

[1] Department of Research Development and Regulatory Affairs, MAPS Public Benefit Corporation, Santa Cruz, CA, United States, [2] Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA, United States, [3] MAPS Public Benefit Corporation, Santa Cruz, CA, United States, [4] Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, United States

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Felix Müller, University Psychiatric Clinic Basel, Switzerland

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***Correspondence:**
Lisa Jerome
ilsa@mapsbcorp.com

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Unsuccessfully treated posttraumatic stress disorder (PTSD) is a serious and life-threatening disorder. Two medications, paroxetine hydrochloride and sertraline hydrochloride, are approved treatments for PTSD by the Food and Drug Administration (FDA). Analyses of pharmacotherapies for PTSD found only small to moderate effects when compared with placebo. The Multidisciplinary Association for Psychedelic Studies (MAPS) obtained Breakthrough Therapy Designation (BTD) from the FDA for 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treatment of PTSD on the basis of pooled analyses showing a large effect size for this treatment. This review covers data supporting BTD. In this treatment, MDMA is administered with psychotherapy in up to three monthly 8-h sessions. Participants are prepared for these sessions beforehand, and process material arising from the sessions in follow-up integrative psychotherapy sessions. Comparing data used for the approval of paroxetine and sertraline and pooled data from Phase 2 studies, MAPS demonstrated that MDMA-assisted psychotherapy constitutes a substantial improvement over available pharmacotherapies in terms of safety and efficacy. Studies of MDMA-assisted psychotherapy had lower dropout rates compared to sertraline and paroxetine trials. As MDMA is only administered under direct observation during a limited number of sessions, there is little chance of diversion, accidental or intentional overdose, or withdrawal symptoms upon discontinuation. BTD status has expedited the development of MAPS phase 3 trials occurring worldwide, leading up to a planned submission seeking FDA approval in 2021.

Clinical Trial Registration: www.ClinicalTrials.gov, identifiers NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610.

Keywords: methylenedioxymethamphetamine, posttraumatic stress disorder, breakthrough therapy, sertraline, paroxetine, anxiety

INTRODUCTION

Breakthrough therapy designation (BTD) is one of the Food and Drug Administration's (FDA) expedited drug development pathways. To be eligible for BTD, a sponsor must demonstrate that the investigational product is intended to treat a serious and life-threatening condition, with preliminary evidence supporting a substantial advantage at a clinically significant endpoint over existing drugs (1). On August 16, 2017, the FDA granted breakthrough therapy designation for MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder (PTSD). This application was among the 45% of applications granted BTD status in 2017 (2). The aim of this review is to summarize the data and rationale presented in the application that led FDA to grant this designation.

PTSD is considered a serious and life-threatening disorder and is associated with increased mortality, cardio-metabolic morbidity, and suicide risk. PTSD negatively impacts a person's daily life, often resulting in fractured relationships, depression, decreased daily functioning, diminished cognitive and psychosocial functioning, substance abuse, and high-cost healthcare utilization ($34.9 billion in inflation-adjusted charges for hospitalizations (2002–2011) (3). Approximately 7% of the U.S. population, and 11.2–17.1% of veterans (4), will have PTSD sometime in their life (5).

Only two drugs, the selective serotonin reuptake inhibitors (SSRIs) sertraline hydrochloride (Zoloft) and paroxetine hydrochloride (Paxil), are approved oral medications for PTSD (6–8). These medications and trauma-focused psychotherapies (e.g., eye movement desensitization, cognitive processing therapy, prolonged exposure) are recommended as first-line treatments for PTSD (9–12). In a meta-analysis evaluating psychotherapy versus pharmacotherapy, trauma-focused psychotherapies resulted in greater and longer lasting improvements than medications (12). Meta-analyses and network meta-analyses found paroxetine, but not sertraline, performed better than placebo (13, 14). Hoskins and colleagues reported that SSRIs had a small effect size with respect to PTSD symptom reduction. When compared to a control group, SSRIs either had insignificant effects or small/moderate effects, while trauma-focused therapies varied from small to large effects (12). The average dropout rate for the 55 studies included in the meta-analysis was 29% (0–79%) demonstrating that many individuals fail to tolerate or respond to available treatments (12), including trauma-focused psychotherapies, where the dropout can range from 28 to 68% (15, 16). A network meta-analysis reported that dropout rate for paroxetine and sertraline was greater than placebo (14).

The Multidisciplinary Association for Psychedelic Studies (MAPS) holds an Investigational New Drug Application (IND) for MDMA as an adjunct to psychotherapy for treatment of PTSD. MAPS has sponsored six phase 2 trials of MDMA-assisted psychotherapy for PTSD that lasted from April 2004 to March 2017. The safety and efficacy results from these trials were submitted to the FDA, along with a summary of the sertraline and paroxetine data that supported the New Drug Application (NDA) for approval of these drugs for the indication of PTSD. Sertraline and paroxetine summary data was extracted from documents found in the FDA drug database, including the Review and Evaluation of Clinical Data and the drug labels (17–20).

Here, we present the evidence included within the breakthrough therapy application showing that MDMA-assisted psychotherapy was superior in phase 2 trials in terms of safety and efficacy compared to the two approved SSRIs for treatment of PTSD. The control groups in the MDMA trials also received intensive psychotherapy (approximately 30 h), while SSRIs pivotal trials used a placebo without any type of therapy for comparison. Since the FDA does not regulate psychotherapy, the BT application did not compare MDMA-assisted psychotherapy to trauma-focused therapies. However, since trauma-focused therapies have evidence for the greatest effectiveness in reducing PTSD symptoms, we have included an additional section in this review comparing MDMA-assisted-psychotherapy with first-line psychological therapies.

EFFICACY AND DURABILITY OF RESPONSE: MDMA VS. SSRIS

MDMA-Assisted Psychotherapy

MDMA is a ring-substituted phenethylamine that is classified as an entactogen in the Merck Index (21) due to its properties that can promote empathy and compassion for self and others. MDMA stimulates release of serotonin, norepinephrine and dopamine, and may act directly on some adrenergic, cholinergic, and serotonergic receptors (22). MDMA elevates levels of the neurohormone oxytocin, an effect likely mediated through direct or indirect action on 5HT1A, 5HT2A, and 5HT4 receptors (23–25), as well as elevating levels of prolactin, arginine vasopressin (AVP), adrenocorticotrophic hormone (ACTH), and cortisol (26–29). MDMA possesses a unique pharmacodynamic profile in humans that includes increased emotional empathy, an increase in feelings of interpersonal closeness, greater prosocial behavior, and an increased ability to tolerate distressing memories, greater reward from pleasant memories, and less distress in response to social exclusion (30–34). Imaging studies found that MDMA reduced activity in brain areas associated with anxiety, including the amygdala, and increased activity in prefrontal cortex (35–37). Hypotheses for MDMA's therapeutic action include enhanced fear extinction, memory reconsolidation, enhanced therapeutic alliance, widening a window of tolerance for distressing thoughts or experiences, and re-opening or enhancing a critical period for experiencing social reward (25, 38, 39). It is likely through these effects that MDMA augments and enhances effectiveness of psychotherapy.

Investigators have developed standardized psychotherapeutic methods for combining MDMA and psychotherapy that include up to 3 sessions with MDMA and up to 12 non-drug sessions. During preparatory sessions participants meet with the two co-therapists, usually one male and one female, when they discuss their goals, and concerns, and learn what to expect during the MDMA-assisted session. The psychotherapy during MDMA-assisted sessions is relatively non-directive, supporting the participants spontaneous experience, and designed to

facilitate processing of challenging emotions in a safe and controlled setting (40–44). Participants may use eye shades, and may listen to a program of music designed to support the therapy. Periods of inner focus alternate with periods of talking to the therapists. Vital signs are assessed periodically. Material arising during MDMA-assisted psychotherapy sessions is integrated in subsequent psychotherapy visits. Subsequently, participants are encouraged to make time to explore and express their unfolding experience using journaling or artwork. Participants in Phase 2 studies were contacted for 7 days after each experimental session. More information concerning MDMA-assisted psychotherapy can be found in publications and in the MDMA Treatment Manual (42). Studies with a long term follow up demonstrate durable improvement in PTSD (41, 43–45), social anxiety in autistic adults (46), and anxiety associated with facing a life threatening illness (22, 38).

Phase 2 Trials of MDMA-Assisted Psychotherapy for PTSD Treatment

The six Phase 2 studies of MDMA-assisted psychotherapy that supported the breakthrough application followed a randomized, double-blind, placebo-controlled design with the Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) as the primary efficacy measure (41, 44, 45, 47, 48). The CAPS-IV is an established measure of PTSD symptoms (49, 50). To enroll, participants were required to have a CAPS-IV total severity score of 50 or greater and to have failed to respond to or tolerate at least one course of treatment. The average duration of PTSD was 17.9 years. The basic study design for the six studies included three preparatory psychotherapy sessions, followed by 2–3 blinded, 8-h experimental psychotherapy sessions with MDMA (75–125 mg) or comparator/placebo (0–40 mg MDMA), and three 90-min non-drug integrative psychotherapy visits following each experimental session. Experimental sessions were scheduled approximately a month apart. Independent Raters (not present during treatment, blinded to group assignment) administered CAPS-IV at baseline, primary endpoint (3–8 weeks after two blinded sessions, or after three sessions in one study), and secondary endpoints (time points during the open-label crossover and at the 12-month follow-up).

Data was pooled across the six phase 2 studies (**Table 1**). Results showed that the active dose group (MDMA 75–125 mg, n = 72) was statistically superior to the control group (0–40 mg, n = 31) at the primary endpoint (independent samples t-test, $p < 0.001$), with average (SD) drop in CAPS-IV total scores −37.8 (29.29) for the active group and −11.6 (17.93) for the control group. There was large between-group Cohen's *d* effect size (0.9).

Prior to enrollment in MAPS-sponsored Phase 2 trials, 17 and 35 subjects (of n = 105) had previously taken paroxetine and sertraline, respectively (**Table 2**). Twelve participants had tried both SSRIs. These individuals did not reach adequate symptom reduction or failed to tolerate the SSRIs. From this subset, 20/38 (52.6%) subjects that received active doses of MDMA (75–125 mg) no longer met criteria for PTSD at the primary endpoint. The average drop in CAPS-IV total scores was −40.1 (25.66) for participants who had previously taken paroxetine and −35.04 (27.5) in participants who had previously taken sertraline (**Table 2**). The other 14 subjects were randomized to the control group. The high response rate and large drops in CAPS-IV total score in this subset suggests that MDMA therapy may be able to effectively treat PTSD in individuals who do not adequately respond to SSRIs.

TABLE 1 | Pooled CAPS-IV data from six phase 2 MAPS-sponsored studies of MDMA-assisted psychotherapy.

	Active group (MDMA 75–125 mg) N = 72	Control group (MDMA 0–40 mg) N = 31
Change in CAPS-IV total scores [a], mean (SD)	−37.8 (29.29)	−11.6 (17.93)
Cohen's *d* effect size[b]	1.5	0.6
Dropouts, n (%)[c]	5 of 74 (6.8%)	3 of 31 (9.7%)

[a]*Change in CAPS-IV scores from baseline to the primary endpoint (1–2 months post 2–3 MDMA sessions).*
[b]*Within-group Cohen's d effect size calculated by dividing the change from baseline to primary endpoint by the standard deviation.*
[c]*For the active group, 3 terminated early but completed an endpoint assessment and 2 terminated early with no endpoint assessments. For the control group, 3 terminated early but completed an endpoint assessment.*

TABLE 2 | Mean change from baseline to the primary endpoint in CAPS-IV total scores in MAPS-sponsored phase 2 subjects who had previously taken sertraline, paroxetine, or both.

	Paroxetine n = 17	Sertraline n = 35	Paroxetine/ sertraline n = 12
Control group, mean (SD) (MDMA 0–40 mg)	−21.0 (24.01) n = 4	−15.9 (16.87) n = 10	−30.3 (18.50) n = 3
Active group (MDMA 75–125 mg)	−40.1 (25.66) n = 13	−35.04 (27.5) n = 25	−38.2 (29.90) n = 9

Sertraline Phase 3 Trials for PTSD

Sertraline was investigated by Pfizer for treatment of PTSD in four studies of similar design with a 12-week flexible dose (50, 100, 150, and 200 mg with 25 mg starting dose for titration) (17, 20). Subjects who met DSM-III-R criteria with a CAPS-2 total score of 50 or greater were enrolled. Patients had a mean duration of PTSD for 12 years and 44% of patients also had a depressive disorder. Two of the four studies failed to find a significant difference between the sertraline and placebo treated groups on any of the primary efficacy outcomes. One study (640, n = 208) reported efficacy on CAPS-2 total score at week 12 [last observation carried forward (LOCF) method, $p = 0.043$] but not week 12 [observed case (OC)] or any earlier weeks. Placebo-subtracted effect size was 0.31, with a 6.8 point mean difference between groups in CAPS-2 total score (LOCF). The other study (671, n = 183) detected efficacy (OC) of sertraline at weeks 2 ($p = 0.041$), 4 ($p = 0.0002$), 6 ($p = 0.011$), 8 ($p = 0.006$),

10 (p = 0.04), and 12 (p = 0.016) on CAPS-2 but only in females which was influenced by mood improvement.

A combined analysis of the two positive studies found a significant difference between sertraline and placebo groups only in women but not in men. Results suggest much of the effect on PTSD scales correlated with improvement in the HAM-D, therefore it is unclear whether sertraline treats PTSD or comorbid depression, an indication the drug was already approved for. The report stated that there was insufficient evidence to support any efficacy claim beyond 3 weeks of treatment. However, a longer-term study that randomized responders (n = 96) in a 24-week open-label continuation trial of sertraline (50–200 mg/day), or switched to placebo for 28 weeks, found significantly reduced relapse rates for the sertraline group, in both males and females.

Paroxetine Phase 3 Trials for PTSD

Paroxetine (20–50 mg/day) demonstrated superiority over placebo on change from baseline for the CAPS-2 total score in two multicenter, placebo-controlled studies in adults who met DSM-IV criteria for PTSD. The trials were sponsored by GlaxoSmithKline (18, 51). In these studies, 858 patients had PTSD symptoms with duration on average of 13 years. Major depressive disorder was present in 41% of patients and non-PTSD anxiety disorder was reported for 40% of patients. Primary outcomes were change from baseline to endpoint on CAPS-2 total score and the proportion of responders assessed by the Clinical Global Impression-Global Improvement Scale (CGI-I), a 3-item observer-rated scale.

In Study 1 (20 and 40 mg) and Study 2 (20 and 50 mg), paroxetine was significantly superior to placebo on both outcome measures. In Study 1 (n = 551), paroxetine was better than placebo (p < 0.001) at 4, 8, and 12-week time points for the LOCF and OC analyses. 71% of 40 mg paroxetine and 76% of 20 mg paroxetine treated patients met response criteria on CGI-I compared to 48% of placebo (p < 0.001). The difference between paroxetine and placebo groups on CAPS-2 total score was approximately 14 units for LOCF and OC analyses for both dose groups. In Study 2 (n = 307), paroxetine was better than placebo (p < 0.001) at 12-week time point for the LOCF and OC analyses. 76% of paroxetine treated patients met response criteria on CGI-I compared to 50% of placebo (p < 0.001). The difference between paroxetine and placebo groups on CAPS-2 total score was approximately 11 units for LOCF and 14 units for OC.

A third study with flexible doses (20–50 mg) found paroxetine to be significantly better than placebo on CAPS-2 total score, but not on CGI-I responders (defined as patients having a score of 1 "very much improved" or 2 "much improved"). In Study 3 (n = 322), CAPS-2 total score was statically superior in paroxetine group compared to placebo for LOCF (p = 0.047) but not OC analysis (p = 0.071) at the 12-week time point. On the CGI-I, 60% of paroxetine treated subjects met response criteria compared to 52% of placebo (not statistically significant). The difference between paroxetine and placebo groups on CAPS-2 total score was approximately 6 units for LOCF and OC analysis. Analyses did not detect any differences in gender on treatment outcomes.

The difference in CAPS-2 total scores between paroxetine and placebo in mean change from baseline at 12 weeks was roughly 6-14 units across the three studies. According to the drug label, the efficacy of paroxetine to treat PTSD beyond 12 weeks had not been investigated in controlled clinical trials, yet PTSD is a chronic condition.

Comparison: SSRIs vs. MDMA

Primary efficacy evaluation of six MAPS-sponsored phase 2 trials on change from Baseline to Primary Endpoint in CAPS-IV Total Severity indicated a significant effect of MDMA over the comparator group (p < 0.001), with a large between-group effect size (0.9 Cohen's *d* effect size) that was approximately double that of paroxetine (0.45–0.56) and triple that of sertraline (0.31–0.37). In comparison of mean change in CAPS total scores, placebo subtracted scores for sertraline ranged from 6.8–9.8 units, for paroxetine 6–14 units, and for MDMA 26.2 units (**Table 3**). The fact that the control group in MDMA studies received the same intensive psychotherapy as the active dose group adds to the clinical significance of these differences. Results from MAPS-sponsored MP-1 study detected significant (p = 0.013) difference between MDMA (125 mg) and placebo groups on CAPS-IV total scores 3–5 days after the first experimental session, demonstrating a rapid clinical response after a single MDMA dose. SSRIs require at least 2 weeks of daily dosing with dose titrations to produce any detectable PTSD symptom improvements, and one pivotal

TABLE 3 | Comparison of sertraline, paroxetine, and MDMA mean CAPS reduction LOCF, intent-to-treat.

	Sertraline		Paroxetine		MDMA	
	CAPS-2 (sertraline–placebo)[a]	Dropout %	CAPS-2 (paroxetine–placebo)[a]	Dropout %	CAPS-IV (MDMA–control)[b]	Dropout %
Study 1	–6.8 (effect size 0.31)	29.3%	–14 (effect size 0.56)	35.5%	–26.2 (effect size 0.9)	7.6%
Study 2	–9.8 (effect size 0.37)	28.4%	–11 (effect size 0.45)	39.0%	—	
Study 3	—		–6 (effect size 0.09)	33.0%	—	

[a]*Effect sizes were not reported in FDA statistical package for paroxetine. Placebo subtracted effect. Size were determined from CAPS scores by calculating the change from baseline divided by the standard deviation.*

[b]*Primary endpoint was 1–2 months after 2–3 blinded experimental sessions.*

study of sertraline and one of paroxetine did not find significant improvement until after 12 weeks of daily drug administration. The beneficial effects of MDMA-assisted psychotherapy have been shown to last for at least 12 months in many participants (67.8% of n = 90 did not meet diagnostic criteria), while paroxetine (12 weeks) and sertraline (3 weeks) drug labels specify that long-term efficacy was not assessed. Sertraline was only shown to statistically significant in women and not men, while MDMA has been effective for both males and females with no difference in response measured

Sertraline and paroxetine demonstrated superiority on the CAPS-2 over placebo in two 12-week pivotal trials which led to a new marketing label for the indication of PTSD. Both had small to medium placebo-subtracted effect sizes (0.31–0.37 and 0.45–0.56, respectively) and require daily dosing for 12 weeks.

COMPLIANCE AND SAFETY: MDMA VS. SSRIS

The dropout rate in active (75–125 mg blinded) MDMA-treated subjects in MAPS-sponsored Phase 2 trials was 6.8% (5 of 74, with 2 excluded for missing outcome data and 3 excluded for early termination, with outcome data), considerably less than SSRI trials where dropout rates were 11.7% in paroxetine-treated and 28% in sertraline-treated subjects, indicating that MDMA is better tolerated by a PTSD population than the two SSRIs. Reduced drop-out rates in MAPS' Phase 2 studies may result from a strong therapeutic alliance, and commitment to the course of psychotherapy, as well as the therapeutic effects of MDMA. On the other hand, dropout rates (3 of 31, 9.7%) were also low for the control group which could reflect some benefit from the psychotherapy alone, or increased motivation to remain in the study to receive active MDMA during the open-label crossover segment.

In paroxetine trials, the most common adverse events (5% or greater and at least 2× that of placebo) in the PTSD population were: asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence. Reported by 19% of subjects, nausea was the most frequently experienced treatment-emergent adverse event. For sertraline, the most common effects were nausea, headache, insomnia, diarrhea, dry mouth, ejaculation failure, somnolence, dizziness, and fatigue.

Administering MDMA in single doses spaced a month apart in a controlled setting has several inherent benefits over chronic daily dosing of paroxetine or sertraline. Firstly, compliance is not an issue in studies of MDMA, because all dosing occurs in a clinic under supervision, whereas SSRIs rely on patients self-administering daily doses which can be a challenge due to cognitive and behavioral impairments that can accompany PTSD (52).

Secondly, fewer side effects are reported after MDMA due to the limited number of administrations. Phase 2 safety data showed that reactions were reported most frequently on the day of MDMA administration and typically diminished in the few days following. The most commonly reported reactions on the day of the experimental session were anxiety, tight jaw/jaw clenching, lack of appetite, headache, and fatigue (48). On the day of blinded experimental sessions, reactions reported by the active MDMA group by at least 2x of the frequency of the control group were diarrhea, difficulty concentrating, dizziness, heavy legs, impaired gait/balance, jaw clenching/tight jaw, lack of appetite, nausea, nystagmus, paresthesia, perspiration, sensitivity to cold, thirst, and weakness. These findings are in line with clinical trials in healthy controls (53, 54). On the other hand, patients taking paroxetine and sertraline experience more prolonged adverse reactions due to steady state drug plasma levels across the 12-week treatment period.

Discontinuation of paroxetine and sertraline may be accompanied by adverse effects (55), likely caused by neuroadaptations of decreased levels of serotonin transporters in neuronal membranes after use of SSRIs (56). For discontinuation of sertraline and paroxetine gradual tapering is recommended, and patients should be monitored for discontinuation emergent symptoms, which can be very troubling. Adverse events during discontinuation (incidence of 2% or greater for paroxetine and at least 2x that of placebo) were abnormal dreams, paresthesia, and dizziness, and for sertraline, they were nausea, insomnia, and diarrhea (18, 20). Post-marketing surveillance identified a number of additional discontinuation emergent negative effects, including sensory disturbances, agitation, anxiety, nausea, and sweating; however causal relationship to drug hasn't been confirmed.

Single doses of MDMA have not produced discontinuation symptoms. Some adverse reactions are reported during the 7 days following an MDMA dose, including anxiety, dizziness, depressed mood, fatigue, headache, jaw clenching or tightness, lack of appetite, nausea, and panic attack (48). By Day 5, the only reactions reported in over 20% of active dose participants were fatigue and anxiety. Both were reported by nearly equal numbers of active and control dose participants. Symptoms were mild to moderate in severity, and nearly all resolved within 7 days of dosing. Eight participants in the active dose group and three in the control group, reported a reaction on the seventh day of follow-up (not seven consecutive days of experiencing the reaction) that was therefore recorded as an adverse event (AE). Reactions fitting AE criteria and reported by more than two participants were anxiety and low mood, occurring in both active and control groups. Both are prominent symptoms of PTSD. Only three participants had the same reaction on day of experimental session and 7 days following the session, which included anxiety, low mood, and muscle tension.

Estimating risk of long-term deleterious effects of discrete doses of MDMA in a controlled setting compared to retrospective studies in people reporting ecstasy use is inappropriate for several reasons. Ecstasy can contain an unknown quantity of MDMA and adulterants, or no MDMA at all, and most people ingesting MDMA are polydrug users. Most studies are retrospective, with only a single prospective study reported detecting signs of a specific impairment in verbal memory in a sample of people reporting nonmedical use, without detecting any functional or structural changes in the brain (57, 58). Systematic reviews of the literature found that most research enrolls people whose lifetime

use far exceeds the average (59–61). In contrast, cognitive function in three trials of MDMA-assisted psychotherapy failed to find impairment after any dose of MDMA (48). When asked about 'ecstasy' use at 12-month follow-up after participation in a Phase 2 trial, eight participants, six of whom had taken ecstasy prior to enrollment, reported having used it one to three times. This indicates that MDMA given in the context of psychotherapy does not have high abuse liability (41, 43, 44, 47, 62).

An additional risk of SSRIs is that they are contraindicated with MAOIs and some other drugs due to inhibition of P450 enzymes. Since these drugs are take-home medications, patients are at risk of accidentally consuming a contraindicated medication that could have serious adverse effects, including death. Accidental and intentional overdoses have been reported with both SSRIs (63). Since clinicians collect concomitant medication information at each session before administering MDMA, the risk for accidental use of a contraindicated medication is far reduced, and risk of overdose is eliminated by dispensing only the recommended dosage by a prescribing physician. Both SSRI drug labels state that alcohol is not recommended, but given that a significant number of people with PTSD also have comorbid alcohol use disorders, refraining from alcohol may be particularly problematic for this population and lead to negative effects (64, 65).

MDMA-assisted psychotherapy received BTD based on its use in treating PTSD, a serious and life-threatening condition, and on the basis of phase 2 clinical data that MDMA produced substantial clinical improvement and greater compliance than the two approved drugs for PTSD, paroxetine and sertraline. Data from Phase 2 provides evidence that PTSD, independent of cause, is treatable with 2 to 3 sessions of MDMA-assisted psychotherapy, and offers a larger treatment effect, increased compliance and lower risk of dropout, reduced possibility of drug interactions compared to paroxetine and sertraline. There have been no deaths related to MDMA in controlled Phase 1 and 2 studies, and if it is approved for clinical use, MDMA will be administered directly to patients, and only in licensed MDMA clinics under controlled conditions similar to those in clinical research. The single-dose regimen of MDMA produces fewer, self-limiting, transient side effects and greater compliance compared to daily dosing of paroxetine and sertraline.

COMPARISON OF MDMA-ASSISTED PSYCHOTHERAPY VS. TRAUMA-FOCUSED THERAPIES

In meta-analyses comparing efficacy of PTSD treatments investigated in randomized controlled trials, trauma-focused psychotherapies generally result in greater and more sustained response than pharmacotherapies and other psychological therapies (12, 66). Lee et al. report comparative effect sizes from meta-analyses of randomized trials that included a control condition, with controls for psychotherapy trials including supportive psychotherapy, biofeedback, and relaxation training, and excluding those with waitlist and treatment-as-usual controls. Compared to control, after 14–27 weeks of trauma-focused therapies the effect size was −0.96. For all medications, which included SSRIs, SNRIs, antiepileptics, antipsychotics, the effect size was −0.44. The magnitude of effect (0.9) of MDMA-assisted psychotherapy is in the range of first-line trauma-focused therapies. MDMA was compared to psychotherapy alone, or low dose MDMA plus psychotherapy, as the control condition and Phase 2 studies enrolled only participants who had previously tried and failed to respond to or tolerate available treatments.

Beyond the quantifiable change of PTSD symptoms, the degree to which MDMA supports the unfolding of a healing experience through neurochemical changes should be considered. Biochemically inducing a mental state more receptive to engaging in deep therapeutic processing could help to speed up symptom improvement or improve treatment outcomes for those resistant to other therapies. There is some evidence from nonclinical experiments that MDMA may increase neuroplasticity through BDNF-dependent mechanism (67), and otherwise alter brain activity in key networks for emotional-memory processing (30). Psychologically, MDMA may ease the challenge of recalling traumatic memories and feeling deeply into the associated emotions. Posttraumatic growth measured by the Posttraumatic Growth Inventory (PTGI), and personality shifts measured by the NEO Personality Profile have been observed after MDMA-assisted psychotherapy (43, 68). In addition, the importance of patient choice regarding therapy for PTSD has been pointed out, and MDMA-assisted psychotherapy may offer advantages in this area if it makes processing trauma less arduous (69).

Another recent meta-analysis paper, found no significant differences in benefits of pharmacological, psychotherapeutic, or the combination at the end of treatment, except at the last available endpoint during long-term follow-up, at which point psychotherapeutic treatments were significantly better than medications. In this analysis, the combined treatments, which included one MDMA-assisted psychotherapy trial, were slightly but not significantly more beneficial than psychotherapeutic treatments alone (66). Data from the other five phase 2 MDMA trials were not included, and the outcome from the MDMA trial was analyzed along with other medication-therapy combinations (e.g., SSRIs and CBT). Until MDMA-assisted psychotherapy is compared to trauma-focused therapies in a randomized trial, it is uncertain whether either approach is superior in terms of efficacy or tolerance. Though it may potentially have greater risks and increased likelihood of mild to moderate adverse events compared with non-drug therapies, MDMA has thus far demonstrated a favorable safety profile with limited administrations in clinical settings. Patient experience of each therapy, time to respond, and durability of response should be evaluated. Future research could also explore whether MDMA combined with existing manualized trauma-focused therapies potentiates PTSD symptom reduction.

STATUS OF MDMA DRUG DEVELOPMENT WITH BREAKTHROUGH DESIGNATION

BTD is intended to expedite the development and approval of promising treatments by allowing for more frequent interactions

with the FDA, rolling review of documents, and the possibility for priority review (6 months rather than the normal 10-month review period) (1). BTD also receives an organizational commitment from the FDA with more guidance and involvement of FDA senior managers for efficient drug development.

After receiving BTD for this program, MAPS and the FDA also reached agreement under the Special Protocol Assessment (SPA) process for the design of two multi-site Phase 3 trials (MAPP1 and MAPP2) of MDMA-assisted psychotherapy for patients with at least severe PTSD. These two pivotal Phase 3 trials will enroll approximately 200-300 participants at sites in the USA, Canada, and Israel.

The pivotal Phase 3 trial started in November 2018. If Phase 3 trials produce significant confirmatory results and satisfactory safety profile, an application for marketing approval of MDMA-assisted psychotherapy for PTSD will be filed with the FDA. Filing of a New Drug Application is projected for 2021, with anticipated approval in 2022.

CONCLUSION

It is anticipated that MDMA, with its unique pharmacological mechanisms combined with psychotherapy, has advantages over existing medications used as first-line PTSD treatments in terms of safety and side effect profiles, efficacy, and length of remission. PTSD is a chronic condition that afflicts a substantial number of individuals who do not adequately respond to available therapies and are at increased risk of suicide, other mental health conditions, cardiovascular disease, and cognitive impairment. Findings from both nonclinical and clinical studies support a novel mechanism by which MDMA amplifies the therapeutic effects of psychotherapy by a dynamic interaction of brain regions, and affiliated neurochemicals therein, known to be involved in fear extinction learning, memory reconsolidation, emotional processing, and cognition (30, 32, 39, 48, 70). With many apparent advantages over existing medications, including efficacy, tolerability, and duration of therapeutic effects, MDMA-assisted psychotherapy has the potential to favorably impact the lives of thousands who suffer from PTSD world-wide.

AUTHOR CONTRIBUTIONS

Concept and review design: LJ, AF, AE, BY-K, RD, and MM. Acquisition, analysis, or interpretation of data: LJ, AF, AE, BY-K, RD, and MM. Drafting of the manuscript: LJ, AF, AE, BY-K, RD, and MM. Critical revision of the manuscript for important intellectual content: LJ, AF, AE, BY-K, RD, and MM. Obtained funding: RD.

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Self-Rated Effectiveness of Microdosing With Psychedelics for Mental and Physical Health Problems Among Microdosers

Nadia R. P. W. Hutten, Natasha L. Mason, Patrick C. Dolder and Kim P. C. Kuypers*

Department of Neuropsychology & Psychopharmacology, Faculty of Psychology & Neuroscience, Maastricht University, Maastricht, Netherlands

Background: There is a growing interest in the use of psychedelic substances for health related purposes, including symptom relief for disorders like anxiety, depression, and pain. Although the focus of recent clinical trials has been on high doses of these substances, anecdotal evidence suggests that low (micro) doses are also effective, and may be more suitable for certain conditions. Nonetheless, empirical evidence regarding the efficacy of microdosing with psychedelics for symptomatic relief is lacking. The present study aimed to investigate, by means of an online questionnaire, the self-rated effectiveness (SRE) of microdosing with psychedelics (MDP) for mental and physiological disorders compared to the conventional prescribed treatment and to regular doses of psychedelics.

Methods: An online questionnaire was launched on several websites and fora between March and July 2018. Respondents who had consented, were 18 years of age or older, had experience with microdosing and were diagnosed with at least one mental or physiological disorder by a medical doctor or therapist (N = 410; 7.2%) were included in the analyses. Odds ratio were calculated to compare the SRE of MDP with conventional treatment, and regular psychedelic doses for mental and physiological diagnoses for each of the three effectiveness questions ("Did it work," "Symptom disappear," "Quality of life improved").

Results: Odds ratio showed that SRE of MDP was significantly higher compared to that of conventional treatments for both mental and physiological diagnoses; and that these effects were specific for ADHD/ADD and anxiety disorders. In contrast, SRE of MDP was lower compared to that of higher, regular psychedelic doses for mental disorders such as anxiety and depression, while for physiological disorders no difference was shown.

Conclusion: This study demonstrates that SRE of MDP to alleviate symptoms of a range of mental or physiological diagnoses is higher compared to conventionally offered treatment options, and lower than regular ('full') psychedelic doses. Future RCTs in patient populations should objectively assess the effectivity claims of psychedelics, and whether these are dose related, disorder specific, and superior to conventional treatments.

Keywords: psychedelics, microdosing, self-medication, symptom alleviation, efficacy, psilocybin, LSD

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****Correspondence:***
Nadia R. P. W. Hutten
nadia.hutten@maastrichtuniversity.nl

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INTRODUCTION

As of the last few years, there has been an increasing visibility and interest in the use of low doses of psychedelics, such as lysergic acid diethylamide (LSD) and psilocybin, for beneficial health-related purposes. Referred to as "microdosing," users report consuming about one tenth of a recreational dose (1, 2), to enhance daily functions, without inducing a profound altered state of consciousness (2–9). While the primary motivation to microdose is indeed to enhance performance, including creativity and mental concentration (10), it is also reported to be used to alleviate psychological and physical symptoms, such as anxiety and headache (10–12). However, empirical evidence regarding the efficacy of microdosing with psychedelics to relieve the aforementioned symptoms is currently lacking.

More extensive evidence on the potential therapeutic value of psychedelic substances has been shown after use of regular (larger) doses which induce typical full effects and a profound altered state of consciousness. Recent clinical studies have suggested that LSD (13), psilocybin (14), ayahuasca (15), and methylenedioxymethamphetamine (MDMA) (16, 17), in combination with psychological support, can provide therapeutic relief for those suffering from post-traumatic stress disorder (PTSD), anxiety, and depression. Additionally, earlier studies demonstrated that psychedelics also provided physical symptom relief, for example in patients with pathologic pain (18). Nonetheless, a psychedelic experience, characterized by acute alterations in perception and cognition, and amplified emotional states (19), may not always be necessary in case of the latter, or not preferable based on individuals' (personality) traits (20) or previous (in)experience with psychedelic substances (21). Furthermore, although physically safe, psychedelic experiences can prove challenging and thus psychological support is encouraged during and after the experience. Taken together, a recreational, full dose can prove costly and impractical for certain disorders, requiring individuals to be supervised in a controlled, clinical environment.

Overall, anecdotal reports and small clinical trials support the potential therapeutic utility of psychedelic substances in reducing symptomatology of a range of mental and physiological disorders. However, it has yet to be shown whether a psychedelic experience as induced by a "full" regular dose is necessary to produce symptom relief, or whether (repeated) sub-perceptual doses have therapeutic potential as well. The present study aimed to investigate, by means of an online questionnaire, the self-rated effectiveness (SRE) of microdosing with psychedelics (MDP) for mental and physiological disorders compared to the conventional prescribed treatment and to regular doses of psychedelics.

METHODS

Design

An online questionnaire was advertised to psychedelic users on several psychedelic websites and fora between March and July 2018. The questionnaire was not explicitly targeted to microdosers, and 'microdosing' was not mentioned in the advert in order to obtain a rate of base rate of microdosing in the psychedelic user groups. To be eligible to fill out the survey, respondents had to be ≥18 years and have experience with a psychedelic substance. After having read the study information and having had the opportunity to ask questions about the study, respondents gave their informed consent in order to continue with the survey. Ethics approval was received from the Ethics Review Committee of Psychology and Neuroscience (ERCPN-177_06_03_2017). Qualtrics was used as the platform to create the survey.

Questionnaire

Demographic Information

Demographic details included age, gender, continent of origin, daily occupation, and the highest level of education. Daily occupation consisted of six pre-set options that respondents could choose from; learning/studying, physical work, computer/office work, working with people, travelling, and creative work. The level of education consisted of three pre-set categories; primary (e.g. elementary school), secondary (e.g. high school, academies, gymnasium) and tertiary education (e.g. university, trade school, college).

Psychedelic Substance Use History

Respondents were asked whether they have had experience with LSD, 1P-LSD, ALD-52/1A-LSD, psilocybin (including psilocybin-containing truffles or mushrooms), ayahuasca, DMT, 5-MeO-DMT, Salvinorin A, Mescaline, MDMA/Ecstasy, NBOMe's, 2C's, or any other psychedelic drug in either a microdose, and/or regular dose, which was defined as having "a full psychedelic experience." Further questions about motivations and side effects of microdosing, as well as the microdosing schedule used are reported elsewhere (10).

Mental and Physiological Diagnoses

Respondents were asked whether a medical doctor or therapist diagnosed them with a psychiatric, neurological, or physical disorder. When affirmed, they were asked which of the pre-set disorders applied: depression, anxiety/panic disorder, attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD), bipolar disorder, schizophrenia, obsessive compulsive disorder (OCD), autism/Asperger syndrome, antisocial behavior disorder, borderline personality disorder, substance abuse disorder, Tourette's, Parkinson's, epilepsy, migraine, cluster headache, multiple sclerosis (MS), and/or chronic pain. Furthermore, they had the option to enter free text in a text box when the disorder was not listed.

Disorders were clustered afterwards into main categories according to the classification system of the two leading diagnostic manuals, the DSM-5 for mental disorders and the ICD-10 for physiological disorders which resulted in 14 sub-categories for mental disorders and 11 sub-categories for physiological disorders (**Table 1**). When free text was entered, the response was manually re-classified in the best matching category.

TABLE 1 | Number (percentage) of diagnoses per sub-category of mental and physiological disorders, further separated into those who received conventional treatment and those who used psychedelics to self-medicate.

Diagnoses	Number (%) of respondents who are diagnosed	Number (%) diagnoses per category	Number (%) of diagnoses that received conventional treatment	Self-medication with a psychedelic substance		
				Number (%) that only microdosed	Number (%) that only used regular dose	Number (%) that used both, microdose and regular dose
Mental disorders (DSM-5 categories)						
Neurodevelopmental disorders	ADHD/ADD 153 (37.3), Autism/Asperger 32 (7.8), Tourette 3 (0.7)	188 (45.6)	140 (74.5)	20 (10.6)	5 (2.7)	55 (29.3)
Schizophrenia spectrum and other psychotic disorders	Schizophrenia 12 (2.9)	12 (2.9)	9 (75.0)	–	2 (16.7)	3(25.0)
Bipolar and related disorders	Bipolar 37 (9.0)	37 (9.0)	28 (75.7)	–	2 (5.4)	10 (27.0)
Depressive disorders	Depression 298 (72.7), PMMD 1 (0.2)	299 (72.9)	260 (87.0)	17 (5.7)	22 (7.4)	206 (68.9)
Anxiety disorders	Anxiety/panic disorders 228 (55.6)	228 (55.6)	181 (79.4)	14 (6.1)	9 (3.9)	92 (40.4)
OCD and related disorders	OCD 27 (6.6)	27 (6.6)	18 (66.7)	2 (7.4)	1 (3.7)	9 (33.3)
Trauma- and stressor-related disorders	PTSD 19 (4.6)	19 (4.6)	15 (78.9)	2 (10.5)	3 (15.8)	6 (31.6)
Feeding and eating disorder	Eating disorder[b] 4 (1.0)	4 (1.0)	3 (75.0)	–	1 (25.0)	1 (25.0)
Sleep-wake disorder	Sleep-wake disorders[a] 4 (1.0)	4 (1.0)	2 (50.0)	–	–	–
Sexual dysfunctions	Erectile dysfunction 1 (0.2)	1 (0.2)	1 (100.0)	–	–	1 (100.0)
Gender Dysphoria	Gender dysphoria 2 (0.5)	2 (0.5)	2 (100.0)	–	1 (50.0)	1 (50.0)
Disruptive, impulse control and conduct disorders	BFRB 1 (0.2)	1 (0.2)	1 (100.0)	–	–	1 (100.0)
Substance-related and addictive disorders	Substance abuse disorder 49 (12.0)	49 (12.0)	30 (61.2)	–	2 (4.1)	19 (38.8)
Personality disorders	Antisocial 10 (2.4), Borderline 20 (4.9), Schizoid personality disorder 1 (0.2), dependent personality disorder 1 (0.2)	32 (7.8)	24 (75.0)	1 (3.1)	3 (9.4)	9 (28.1)
Physiological disorders (ICD-10 categories)						
II C00-D48 Neoplasms	Cancer 2 (0.5), Hodgkin's lymphoma 1 (0.2)	3 (0.7)	2 (66.7)	–	–	–
IV E00-E90 Endocrine, nutritional and metabolic diseases	Hashimoto's thyroiditis 1 (0.2)	1 (0.2)	1 (100.0)	–	–	–
V F00-F99 Mental and behavioral disorders	Post-concussive syndrome 1 (0.2)	1 (0.2)	–	–	–	–
VI G00-G99 Diseases of the nervous system	Epilepsy 12 (2.9), Parkinson 2 (0.5), MS 1 (0.2), Cluster headaches 15 (3.7), Migraines 60 (14.6), Chronic pain 56 (13.7), Daily persistent headache 1 (0.2), Dystonia 1 (0.2)	148 (36.1)	96 (64.9)	7 (4.7)	10 (6.8)	30 (20.3)
VII H60-H95 Diseases of the ear and mastoid process	Almost deaf 1 (0.2)	1 (0.2)	1 (100.0)	–	–	–
XI K00-K93 Diseases of the digestive system	Crohns disease 2 (0.5), IBS 2 (0.5)	4 (1.0)	2 (50.0)	–	–	1 (25.0)
XII L00-L99 Diseases of the skin and subcutaneous tissue	Lupus erythematosus 1 (0.2)	1 (0.2)	1 (100.0)	–	–	1 (100.0)

(Continued)

TABLE 1 | Continued

Diagnoses	Number (%) of respondents who are diagnosed	Number (%) diagnoses per category	Number (%) of diagnoses that received conventional treatment	Self-medication with a psychedelic substance		
				Number (%) that only microdosed	Number (%) that only used regular dose	Number (%) that used both, microdose and regular dose
XIII M00-M99 Diseases of the musculoskeletal system and connective tissue	Fibromyalgia 2 (0.5)	2 (0.5)	2 (100.0)	–	–	1 (50.0)
XVII Q00-Q99 Congenital malformations, deformations and chromosomal abnormalities	Ehlers Danlos Syndrome 1 (0.2)	1 (0.2)	1 (100.0)	–	–	–
XIX S00-T98 Injury, poisoning and certain other consequences of external causes	Food sensitivities 1 (0.2)	1 (0.2)	1 (100.0)	–	–	1 (100.0)
Non-classified disorders	Daytime sleepiness 1 (0.2)	1 (0.2)	1 (100.0)	–	–	–

Effectiveness of Conventional Prescribed Treatment

When respondents indicated to have been diagnosed with a specific mental or physiological disorder, they were asked whether they were offered treatment for that particular disorder. In case answers were affirmative (medication, therapy, or both) these questions were followed by three extra questions about treatment efficacy which could be answered negative ("definitely not," "probably not") or positive ("probably yes," "definitely yes"). The questions were "Do you feel the treatment worked," "Did the symptoms disappear to an extent at which daily functioning was not compromised any longer," and "Did your quality of life improve."

Effectiveness of Psychedelic Self-Medication

Respondents were asked whether they have used a psychedelic in order to treat their diagnosed disorder. When affirmative, this was followed by a question which psychedelic substance they used to alleviate the symptoms of the particular disorder, with pre-set options: LSD, 1P-LSD, ALD-52/1A-LSD, psilocybin, ayahuasca, DMT, 5-MeO-DMT, Salvinorin A, Mescaline, MDMA/Ecstasy, NBOMe's, 2C's or any other psychedelic substance. Followed by the question whether they used the substance in a microdose, a regular dose, or both. Additionally, the same three questions about treatment efficacy — as those asked for conventional treatment — were asked per psychedelic substance and dosing ('micro' and/or regular).

Statistical Analysis

Data entered the statistical program SPSS (version 24.0). Respondents who did not give their consent, were not 18 year or older, did not complete the questionnaire, did not have microdosing experience, and did not have any mental and/or physiological diagnosis were excluded (N = 5,271) from the analyses. Frequencies are reported for gender, education, continent of origin, daily occupation, and psychedelic drug use history. Mean (± *SD*) is given for age.

Frequencies are reported for the total number of mental and physiological diagnoses in general, and more specific, per sub-category, for conventional treatment, the use of self-medication with a microdose, a regular dose, and both. The most frequently used psychedelics for self-medication are also reported.

To compare the effectiveness of self-medication with psychedelic microdoses with conventional treatment, and regular psychedelic doses, binary logistic regressions were conducted for the mental (total) and physiological (total) diagnoses for each of the three effectiveness questions. This resulted in odds ratio (OR) values for the three questions. In case of significant results, separate binary logic regressions were conducted for each category within the mental or physiological diagnosed group in order to examine whether this effect was disorder-specific.

Even though ADHD/ADD and autism/Asperger's are both placed in the same category of 'neurodevelopmental disorders' in the DSM-5, the core symptoms of both disorders are different. The scope symptoms of ADHD/ADD are defined as having impairments in attention, impulse control, and hyperactivity; while symptoms of autism/Asperger's are defined as having deficits in social communication and interaction, and restricted repetitive behavior (22–24). Therefore, *ad hoc* analyses have been conducted in order to examine whether ADHD/ADD and/or autism/Asperger's account for the results of neurodevelopmental disorders. When cell count was less than 10 events per independent variable (EVP), no regression was conducted (26). For each OR, 95% confidence intervals (CIs) are given and statistical significance was set at $p = 0.05$. An OR of 1.5 is defined as small, as medium, and 3 as large (Sullivan and Feinn, 2012).

RESULTS

Demographic Information

In total, 3,590 out of 5,681 respondents consented, were 18 years or older, and completed the questionnaire. It took respondents about 16 min to complete the questionnaire, depending on the number of psychedelic substances a person had ever used before, whether they microdosed and whether they were diagnosed

with a disorder. One third (N = 1,116; 31.1%) of the respondents indicated to have microdosed with at least one psychedelic substance. More than one-third (N = 410; 36.7%) of the microdosers indicated to have been diagnosed with at least one mental or physiological disorder by a medical doctor or therapist, the remaining 1,414 respondents who did not microdose and/or were not diagnosed with a disorder were removed from further analyses. Group demographics and detailed drug use history for the whole sample are presented separately, see Hutten et al. (10).

Respondents' mean (± *SD*) age was 28.9 (± 10.1) years with a maximum age of 72 (N = 1); 306 (74.6%) were males aged on average 29.1 (± 10.4) years, 94 (22.9%) females aged on average 28.8 (± 9.3) years, and 10 (2.4%) classified themselves as "other" and had an average age of 25.1 (± 5.9) years. Most of them attended tertiary education (N = 290; 70.7%), the prevailing daily occupation was learning/studying (N = 124; 30.2%), and the majority of our sample originated from North-America (N = 276; 67.3%).

The highest level of education for the other one third of the sample was primary (N = 6; 1.5%) and secondary (N = 114; 27.8%). Other continents of origin were Europe (N = 103; 25.1%), Australia (N = 16; 3.9%), Asia (N = 6; 1.5%), South-America (N = 5; 1.2%) and Africa (N = 4; 1.0%), and daily occupation of the others in the sample consisted of computer/office work (N = 99; 24.1%), working with people (N = 65; 15.9%), physical work (N = 53; 12.9%), creative work (N = 59; 14.4%), and travelling (N = 3; 0.7%); 1.7% (N = 7) did not answer this question.

All microdosers reported to have had experience with regular doses of psychedelics, of which psilocybin (N = 355; 86.6%), LSD (N = 325; 79.3%), and MDMA/ecstasy (N = 263; 64.1%) were the most frequently reported. The most frequently reported psychedelics for microdosing were psilocybin (N = 248; 60.5%), LSD (N = 231; 56.3%), and 1P-LSD (N = 43; 10.5%).

Mental and Physiological Diagnoses

In total, there were 901 mental diagnoses and 161 physiological diagnoses reported. This total number (1,062) is higher than the included sample (N = 410) of microdosers because the majority (N = 298; 72.7%) indicated to be diagnosed with more than one disorder. The average number of diagnoses among the respondents was 2.5 diagnoses. A minority (N = 9; 2.2%) did not disclose the exact disorder they were diagnosed with.

The three most prevalent mental diagnosed disorders in descending order are depressive disorders (N = 298; 72.7%), anxiety disorders (N = 228; 55.6%), and ADHD/ADD (N = 153; 37.3%). The three most prevalent physiological diagnosed disorders are migraines (N = 60; 14.6%), chronic pain (N = 56; 13.7%), and cluster headaches (N = 15; 3.7%). The number of diagnoses per sub-category are presented in **Table 1**.

TREATMENT

The majority of mental diagnoses [number of diagnoses (N) = 714; percentage (%) = 79.2] were prescribed conventional (non)pharmacological treatments. Psychedelics were used to self-medicate in more than half of the mental diagnoses (N = 520; 57.7%) of which the majority refers to both a regular dose and microdose (N = 413; 79.4%). In the other one-fifth of mental diagnoses only a microdose (N = 56; 10.8%) or only a regular dose (N = 51; 9.8%) was used to self-medicate.

The most reported psychedelics used to self-medicate for mental disorders in descending order are: psilocybin (N = 297; 57.1%), LSD (N = 248; 47.7%), and 1P-LSD (N = 68; 13.1%) in microdoses, and psilocybin (N = 336; 64.6%), LSD (N = 264; 50.8%), and MDMA (N = 115; 22.1%) in regular doses.

The majority of physiological disorders (N = 123; 76.4%) were treated with conventional therapy. In one-third (N = 51; 31.7%) of the cases psychedelics were used to self-medicate of which the majority was both with a microdose and a regular dose (N = 34; 66.7%); the remainder self-treated with only a microdose (N = 7; 13.7%) or a regular dose (N = 10; 19.6%). The most reported psychedelics used in order to self-medicate for these phsychological disorders in descending order are: psilocybin (N = 28; 54.9%), LSD (N = 14; 27.5%), and DMT (N = 3; 5.9%) in microdoses; and psilocybin (N = 30; 58.8%), LSD (N = 20; 39.2%), and MDMA (N = 4; 7.8%) for regular doses.

Details of the treatment sub-categories are presented in **Table 1**.

Effectiveness of Psychedelic Microdosing Compared to Conventional Treatment

Binary logistic regression analysis demonstrated that SRE of MDP to treat mental disorders was rated significantly higher compared to that of the conventional, prescribed treatment as indicated by statistically significant OR for the three questions OR (did it work) = 2.77 (p < 0.01; 95% CI [2.19, 3.50]); OR (symptoms disappear) = 2.48 (p < 0.01; 95% CI [1.97, 3.10]), OR "QOL improved" = 2.30 (p < 0.01; 95% CI [1.82, 2.90]) (**Figure 1A**).

Separate binary logistic regressions per mental sub-category showed that MDP was only more effective than conventional therapy for neurodevelopmental and anxiety disorders. Ad hoc analyses of neurodevelopmental disorders revealed that the MDP was rated more effective than conventional therapy for diagnoses of ADHD/ADD, while there were no significant results in the autism/Asperger's category. For the other listed mental disorders statistical significance was either not proven for all three questions (**Table 2**) or it was not possible to calculate due to the low cell count (this was the case for six sub-categories: e.g. trauma- and stressor-related disorders; feeding and eating disorders; sleep-wake disorders; sexual dysfunctions; gender dysphoria; and disruptive, impulse control and conduct disorders).

In addition, binary logistic regression analysis demonstrated that SRE of MDP to treat physiological disorders was significantly higher compared to that of conventional treatment as indicated by statistically significant OR for the three questions OR "did it work" = 6.14 (p < 0.01; 95% CI [2.54, 14.86]); OR "symptoms disappear" = 7.74 (p < 0.01; 95% CI [3.41, 17.59]); and OR "QOL improved" = 4.36 (p < 0.01; 95% CI [1.87, 10.16]), **Figure 1B**).

A separate binary logistic regression for the sub-category 'diseases of the nervous system' of the physiological disorders revealed that MDP was rated to be more effective compared to conventional treatment as indicated by statistically significant

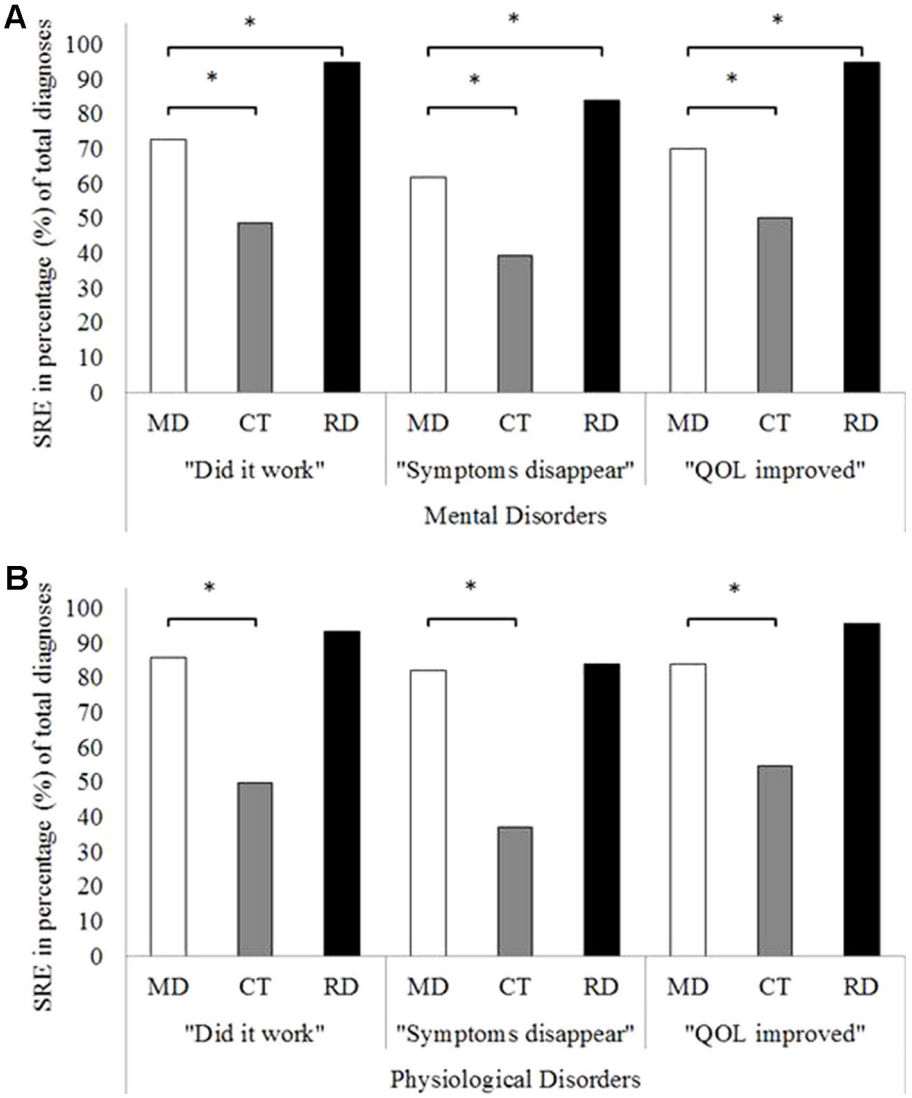

FIGURE 1 | Overall self-rated effectiveness of psychedelic microdoses, conventional treatment, and regular doses of a psychedelic on the three effectiveness questions for mental disorders **(A)** and for physiological disorders **(B)**. *Signifies statistically significant binary logistic regression $p < 0.05$. SRE, self-rated effectiveness; MD, microdose; CT, conventional treatment; RD, regular dose.

OR for the three questions OR "did it work" = 6.78 ($p < 0.01$; 95% CI [2.63, 17.49]); OR "symptoms disappear" = 7.71 ($p < 0.01$; 95% CI [3.23, 18.38]); and OR "QOL improved" = 4.59 ($p < 0.01$; 95% CI [1.87, 11.31]). For all other listed physiological disorders binary logistic regression was not possible to calculate due to the low cell count.

Effectiveness of Psychedelic Microdoses Compared to Regular Doses

Binary logistic regression analysis demonstrated that MDP was rated as less beneficial compared to regular doses for mental disorders as indicated by statistically significant OR for the three questions (OR "did it work" = 0.15 ($p < 0.01$; 95% CI [0.10, 0.24]); OR "symptoms disappear" = 0.31 ($p < 0.01$; 95% CI [0.23, 0.42]); and OR "QOL improved" = 0.13 ($p < 0.01$; 95% CI [0.08, 0.21], **Figure 1A**). However, separate binary logistic regressions per sub-category showed that self-medication with microdoses were statistically less efficacious than regular psychedelic doses for depressive and anxiety disorders on all three effectiveness questions (see **Table 2**) or it was not possible to calculate due to the low cell count (this was the case for six sub-categories: e.g. trauma- and stressor-related disorders; feeding and eating disorders; sleep-wake disorders; sexual dysfunctions; gender dysphoria; and disruptive, impulse control and conduct disorders).

Binary logistic regression analysis also demonstrated that there was no difference in SRE when comparing microdoses and regular doses to treat physiological disorders as indicated by statistically non-significant OR for the three questions (OR "did it work" = 0.45 ($p = 0.27$; 95% CI [0.12, 1.86]); OR "symptoms disappear" = 0.86 ($p = 0.79$; 95% CI [0.29, 2.55]); and OR "QOL improved" = 0.25 ($p = 0.09$; 95% CI [0.05, 1.25]; **Figure 1B**).

TABLE 2 | The odds ratio for SRE of MDP compared to conventional treatment and regular doses compared for each of the three effectiveness questions per sub-category of mental disorders[a].

	"Did it work?"		"Symptoms disappeared?"		"QOL improved?"	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Microdose compared to conventional therapy						
Neurodevelopmental disorders	4.33 (2.06, 9.12)	<0.01	2.56 (1.47, 4.46)	<0.01	3.63 (1.87, 8.05)	<0.01
ADHD/ADD	11.66 (3.46, 39.34)	<0.01	3.40 (1.77, 6.52)	<0.01	8.62 (3.23, 22.98)	<0.01
autism/asperger	6.25 (0.64, 60.94)	0.12	2.67 (0.61, 11.70)	0.19	1.81 (0.35, 9.24)	0.48
Bipolar and related disorders	4.62 (1.06, 20.01)	0.04	4.00 (0.92, 17.33)	0.06	3.47 (0.80, 15.03)	0.10
Depressive disorders	1.89 (1.34, 2.66)	<0.01	1.87 (1.32, 2.64)	<0.01	1.35 (0.96, 1.89)	0.09
Anxiety disorders	6.06 (3.50, 10.44)	<0.01	4.59 (2.78, 7.59)	<0.01	5.78 (3.35, 9.98)	<0.01
OCD and related disorders	3.33 (0.68, 16.29)	0.14	4.16 (0.91, 19.03)	0.07	1.43 (0.32, 6.49)	0.64
Substance-related and addictive disorders	3.94 (1.07, 14.44)	0.04	1.34 (0.43, 3.14)	0.61	5.54 (1.35, 22.77)	0.02
Personality disorders	5.91 (1.06, 32.92)	0.04	5.00 (1.07, 23.46)	0.04	7.86 (0.87, 71.06)	0.07
Microdose compared to regular dose						
Neurodevelopmental disorders	1.30 (0.48, 3.52)	0.61	1.53 (0.76, 3.05)	0.23	0.52 (0.18, 1.53)	0.23
ADHD/ADD	5.33 (1.32, 21.52)	0.02	2.24 (0.97, 5.14)	0.06	1.77 (0.48, 6.53)	0.40
autism/asperger	<0.01 (0.00, 0.00)	0.99	1.36 (0.29, 6.42)	0.70	<0.01 (0.00, 0.00)	0.99
Bipolar and related disorders	0.40 (0.36, 4.47)	0.46	0.40 (0.04, 4.47)	0.46	0.40 (0.04, 4.47)	0.46
Depressive disorders	0.03 (0.01, 0.08)	<0.01	0.14 (0.09, 0.22)	<0.01	0.04 (0.02, 0.09)	<0.01
Anxiety disorders	0.15 (0.04, 0.50)	<0.01	0.26 (0.12, 0.60)	<0.01	0.25 (0.09, 0.68)	<0.01
OCD and related disorders	0.83 (0.11, 6.26)	0.86	0.69 (0.12, 3.96)	0.67	0.56 (0.08, 3.94)	0.56
Substance-related and addictive disorders	0.75 (0.15, 3.84)	0.73	0.29 (0.07, 1.31)	0.11	0.32 (0.03, 3.32)	0.34
Personality disorders	0.50 (0.04, 6.44)	0.60	0.67 (0.09, 4.99)	0.69	1.10 (0.06, 20.01)	0.95

QOL, quality of life; OR, Odds Ratio; CI, confidence interval; ADHD/ADD, attention deficit hyperactivity disorder/attention deficit disorder; OCD, obsessive-compulsive disorder.
[a]Diagnoses with cell count less than 10 are not reported.

DISCUSSION

The present study aimed to investigate, by means of an online questionnaire, the self-rated effectiveness (SRE) of self-medication with psychedelic microdoses for diagnosed mental and physiological disorders, compared to conventional treatments and regular doses of psychedelics. Overall, findings showed that SRE of MDP on all three effectiveness questions ("Did it work?", "Did symptoms disappear?", "Did your quality of life improve?") was higher compared to that of conventional treatments for both mental and physiological diagnoses. In contrast, SRE of microdoses was lower compared to that of regular psychedelic doses for mental disorders, while for physiological disorders no difference was shown. Of note, the aforementioned effects were shown to be disorder specific. Specifically, compared to conventional treatments, further analysis demonstrated that MDP was only rated more beneficial on all three effectiveness questions for neurodevelopmental and anxiety disorders, *ad hoc* analyses revealed that only ADHD/ADD accounted for the results for neurodevelopmental disorders. Whereas compared to regular doses of psychedelics, MDP was rated to be less beneficial on all three effectiveness questions only for depression and anxiety.

The current survey demonstrates that self-medication with MDP was experienced to be more effective compared to conventional treatment in case of anxiety, ADHD/ADD, and physiological disorders such as pain. These findings are in line with anecdotal reports and interview studies reporting the use of psychedelic microdoses to substitute conventional prescribed medications (11, 12, 26). As no experimental comparison between MDP and conventional (non) pharmacological treatments for disorders exists, one can only speculate about the reasons why MDP is found to be more effective. First, MDP produces potentially less unwanted effects compared to conventional pharmacological treatments. For instance, users reported that their traditional stimulants for ADHD cause a crash after use while MDP did not (26). Additionally, compared to traditionally offered medications which are taken daily or even several times a day, microdosers do not usually consume the substance daily (2, 10), thus reducing potential costs and side effects, and even potentially reducing the number of reminders to the patient of being ill.

Although the three effectiveness questions ('worked', 'disappeared', 'QOL') were only statistically significant when MDP was used for anxiety, ADHD/ADD and physiological disorders, other disorders such as depressive, bipolar, substance-related and personality disorders were rated as effective on some of the questions, e.g., depression ('worked' and 'disappeared'), bipolar ('worked'), substance-related ('worked' and 'QOL'), and personality ('worked' and 'disappear'). Interestingly, OCD was not rated to be more effective on any of the questions compared to conventional treatments, and while anecdotal evidence is inconclusive about the effects of MDP on OCD (27), this might indicate that MDP is not effective in treating OCD. In order to understand these differences in SRE of MDP for different disorders, RCTs are needed to objectively examine the reported effects as well as the underlying mechanisms. This knowledge is necessary in the case that psychedelics are approved for therapeutic use for specified indications like PTSD (MDMA) and depression (psilocybin), and off-label prescriptions are being considered.

When comparing SRE of MDP and regular doses of psychedelics, it was found that microdoses were rated to be less effective than regular doses when self-medicating for depression and anxiety, whereas no difference was found for other disorders such as neurodevelopmental disorders, OCD related or physiological disorders such as chronic pain. The finding that only these two

disorders were 'dose-specific' is interesting in light of recent clinical studies. Specifically, clinical trials assessing the efficacy of full, regular doses of psychedelics on treatment resistant depression (28) and end of life depression and anxiety (13, 29, 30) have found an association between the acute quality of the experience (including occurrence of profound psychological 'peak' or 'mystical' experiences), and long-term (positive) clinical outcomes. It could thus be suggested that the acute psychedelic experience is a valued or even necessary aspect of psychedelic-assisted therapy in treating depression and anxiety disorders, and would help explain why doses too low to induce a noticeable change in consciousness would be rated as less effective. Furthermore, as a dose-specific difference in SRE of neurodevelopmental and physiological disorders was not seen, it could be hypothesized that such an experience is not necessary for these disorders, suggesting a different mode of therapeutic action. However, future clinical studies need to properly assess this, as well as further explore whether effects are specific and not due to other currently unmeasured components of psychedelic therapy (28), and investigate the neurobiological mechanisms underlying the acute quality of the experience.

This study is not without its limitations. As our population of interest were recreational psychedelic users, it might not be a representative sample in terms of prevalence of mental disorders. However, data shows that these rates were in line with the general population worldwide (31), with most frequently diagnosed disorders in our sample being stress-related disorders, i.e., depression (N = 299; 72.9%) and anxiety (N = 228; 55.6%). Furthermore, complex mental comorbidity was the rule rather than the exception while the majority (72.7%) of our sample indicated to be diagnosed with more than one disorder, which is also the case in the 'general' psychiatric population (32).

Additionally, comparison of effectiveness of different kind of psychedelics was not possible due to the low cell count for some of the separate substances. Future studies might focus on the effectiveness of LSD compared to psilocybin, for example, as anecdotal reports state that microdosing with LSD produces more stimulating effects compared to psilocybin (11). LSD could therefore be less suited in the treatment of anxiety disorders, as anxiety is already a state of hyperarousal (33), and more suitable in disorders characterized by biological hypo-arousal which is the case in ADHD (34). In addition, the sample was too small in order to make a comparison between microdosing and the different kind of offered treatments, such as medication or therapy sessions.

Moreover, disorder history (duration and severity) were not assessed, so it cannot be established whether microdosing was rated to be more effective for more or less severe cases. Additionally, the duration of symptom alleviation was not asked, it might be that conventional treatment only lasts for one day, microdosing might only last for a couple of days, while regular doses might relieve symptoms up to several months. Finally, as the survey was presented on psychedelic fora, the self-selected sample might have been biased towards the favorability of psychedelics over all kinds of treatments. Thus, the results should be interpreted with caution, and used for rationale to further assess indications of therapeutic potential of psychedelic substances.

To conclude, this study demonstrates that SRE of MDP to alleviate symptoms of a range of mental or physiological diagnoses is higher compared to conventionally offered treatment options and lower than regular ('full') psychedelic doses. Future RCTs in patient populations will be able to answer questions of these effectivity claims of psychedelics, whether these are dose related, disorder specific, and superior to conventional treatments.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Review Committee of Psychology and Neuroscience, Maastricht University, Maastricht, the Netherlands. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KK, NM, and PD designed the study. NM collected the data. NH analyzed the data. NH, NM, and KK wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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No Influence of Dopamine System Gene Variations on Acute Effects of MDMA

*Patrick Vizeli and Matthias E. Liechti**

Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel, Basel, Switzerland

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is a recreational substance also investigated as medication for posttraumatic stress disorder. Dopamine (DA) system stimulation likely contributes to the acute mood effects of amphetamines, including MDMA. Genetic variants, such as single-nucleotide polymorphisms (SNPs), and polymorphic regions of the DA system genes may in part explain interindividual differences in the acute responses to MDMA in humans. We characterized the effects of common genetic variants within genes coding for key players in the DA system including the dopamine D2 receptor (DRD2/ANKK1 rs1800497, DRD2 rs6277, and rs107959), the dopamine transporter (DAT1 rs28363170, rs3836790, rs6347, rs11133767, rs11564774, rs460000, and rs463379), and dopamine D4 receptor [DRD4, variable-number tandem repeat (VNTR)] on the subjective and autonomic response to MDMA (125 mg) in pooled data from randomized, placebo-controlled, crossover studies in a total of 149 healthy subjects. Plasma concentrations of MDMA were used as covariate in the analysis to control for individual pharmacokinetic (metabolic and weight) differences. None of the tested genetic polymorphisms within the DA system altered effects of MDMA when adjusting for multiple comparisons. Genetic variations in genes coding for players of the DA system are unlikely to explain interindividual variations in the acute effects of MDMA in humans.

Keywords: dopamine, SCL6A3, DAT1, DRD2, DRD4, MDMA

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Matthew W. Johnson, Johns Hopkins University, United States

Reviewed by:
Sean Dolan, Johns Hopkins University, United States
Zach Walsh, University of British Columbia Okanagan, Canada

****Correspondence:***
Matthias E. Liechti
matthias.liechti@usb.ch

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INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA; ecstasy) is widely used recreationally for its euphoric effects. Additionally, recent investigations are looking into MDMA as a medication to assist psychotherapy in patients with posttraumatic stress disorder (PTSD) (1–3). MDMA acts mainly as a releaser and reuptake inhibitor of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) *via* an interaction with the respective transporter (4–7). The subjective effects of MDMA have been shown to mainly depend on transporter-mediated release of 5-HT and NE (8). In animals, however, the possibility was raised that the importance of interaction with the DA system would increase with the amount of drug taken (9). To what extent DA is mediating the acute effects of MDMA in humans is unclear. For example, the positive effects of MDMA were diminished after pharmacological inhibition of DA receptors with haloperidol (10). In addition, MDMA-induced hyperactivity was reduced in knockout mice without the DA receptor D_2 gene (DRD2) (11). However, in contrast to the strongly diminished effect of MDMA in subjects with a blocked serotonin transporter, preventing the interaction of MDMA with the DA transporter

(DAT) by pretreatment with bupropion or methylphenidate had no effect on the acute mood effects of MDMA in humans (12–15). Studies on the influence of genetic polymorphisms in the DA system could add adjuvant information to this matter and may also explore the role of the DA system in the interindividual differences in the response to MDMA. So far, only genetic variations of the enzymes that are involved in MDMA metabolism (mainly CYP2D6) displayed a robust influence on MDMA plasma levels in several clinical studies (16–18) and also showed a concomitant modulation of the pharmacodynamic effects of MDMA. However, genetic variants of pharmacological targets of MDMA may also alter its pharmacodynamic effects. A few studies explored the role of genetic polymorphisms of the 5-HT, NE, and oxytocin systems and found only minimal influences on acute effects of MDMA (19–23).

The DAT is a key target for many stimulant-type drugs, including cocaine, amphetamine, methylphenidate, and MDMA (6, 24). Additionally, the transporter is involved in various psychiatric disorders and treatment approaches (25–27). Subsequently, genetic polymorphisms within the single copy gene coding for the DAT (DAT1, SLC6A3) were investigated in relation to cocaine dependence and abuse, methamphetamine psychosis, attention-deficit/hyperactivity disorder (ADHD) and treatment, and bipolar disorder (28–36). Two common variable-number tandem repeat (VNTR) polymorphisms were most extensively studied. One, the rs28363170, is located in the 3′ untranslated region (3′UTR) of the DAT1 gene and exhibits 9 or 10 repeats as most common forms (37). Homozygous carriers of the 9-repeat allele were found to be at a higher risk for persistent ADHD, and the 10/10 genotype was associated with ADHD in children (38). Subjects with the 9/9 genotype were less susceptible to the subjective effects of amphetamine (39). However, carriers of at least one 9-repeat allele showed higher ratings of "high," "any drug effect," "anxious," and "stimulated" after cocaine (40). Conversely, homozygous 10-repeat carriers in combination with a 5-repeat allele of the other extensively studied VNTR in the DAT1, the rs3836790, displayed a lower response to "good drug effects," "bad drug effects," "depressed," and "anxious" (40). The rs3836790 VNTR is located in intron 8 of the human DAT1 gene. The most common forms of this VNTR are 5 or 6 repeats (30). A study in a Brazilian sample found a positive association of the 6-repeat allele and cocaine addiction (28). In contrast, another yet smaller case-control study in a Spain sample showed an overrepresentation of the 5/5 genotype in cocaine abusers (33).

MDMA also directly and indirectly interacts with DA receptors (4). Especially the inhibition of the D_2 with haloperidol showed a significant reduction in MDMA positive effects (10). MDMA-unrelated pharmacogenetic studies showed a positive association of the minor allele of the DRD2 single-nucleotide polymorphisms (SNPs) rs1079597 and rs1800497 with heroin dependence (41), rs6277 and rs1800497 with nicotine dependence (42), and rs6277 with alcohol dependence in males (43). The VNTR polymorphism within the gene coding for the subtype 4 of the DA receptors (DRD4) is also frequently studied in relation to psychiatric disorders and personality traits (44–47). DRD4 VNTR variations range from 2 repeats to 10 repeats, with 4 and 7 repeats as the most frequent forms (48). The presence of a 7-repeat allele has been linked with personal traits like high novelty seeking, risky decision making, and broad sexual interest (44, 47). Moreover, children and adolescents suffering from ADHD and carrying the 7-repeat allele had to take higher doses of methylphenidate to reach sufficient efficacy (49). This finding is in line with earlier results from an *in vitro* study showing a reduced sensitivity of the 7-repeat allele toward DA compared with the 2- and 4-repeat allele (50).

The present study is the first to explore the influence of variants within genes coding for the DA system on the acute effects of MDMA in humans. We analyzed DRD2/ANKK1 rs1800497, DRD2 rs6277, and rs107959, DAT1 rs28363170, rs3836790, rs6347, rs11133767, rs11564774, rs460000, and rs463379, DRD4 VNTR and their influence on acute subjective and autonomic effects of MDMA. Given the partially inconclusive pharmacogenetic studies in addition to the unclear degree to which MDMA effects are driven by the interaction with the DA system, we hypothesized that genetic mutations of the DA system would not influence cardiostimulant effects and have only minimal influence on the mood effects of MDMA.

METHODS

Study Design

This was a pooled analysis of nine double-blind, placebo-controlled, crossover studies that used similar methods and were conducted in healthy subjects and in the same laboratory (14, 15, 51–55). The studies included a total of 164 healthy subjects. Seven studies included 16 subjects each, for a total of 112 subjects, who received 125 mg MDMA twice, once alone and once after pretreatment with a medication (14, 15, 51–54). Two additional studies included 24 and 28 subjects who received 125 mg MDMA alone, placebo, or other treatments (55; Holze et al., unpublished). In the present analysis, only data from the MDMA-alone and placebo sessions were used. In all of the studies, the washout periods between single-dose administrations of MDMA were at least 7 days to exclude possible carryover effects. The studies were all registered at ClinicalTrials.gov (NCT00886886, NCT00990067, NCT01136278, NCT01270672, NCT01386177, NCT01465685, NCT01771874, NCT01951508, and NCT03019822). All of the studies were approved by the local ethics committee and, if necessary, Swiss Agency for Therapeutic Products (Swissmedic). The studies were conducted in accordance with the Declaration of Helsinki. MDMA administration in healthy subjects was authorized by the Swiss Federal Office for Public Health (BAG), Bern, Switzerland. Written informed consent was obtained from all of the participants. All of the subjects were paid for their participation. Detailed pharmacokinetic and safety data from these studies have been reported elsewhere (17, 18, 56). Test sessions were conducted in a quiet hospital research ward with no more than two research subjects present per session. The participants were comfortably lying in hospital beds and were mostly listening to music and not engaging in physical

activities. MDMA was given without food in the fasting state in the morning at 8:00–9:00 AM. A small standardized lunch was served at 12:00–1:00 PM.

Subjects

A total of 164 healthy subjects of European descent, 18–45 years old (mean ± SD = 25.3 ± 4 years), were recruited from the University of Basel campus and participated in the study. One genotyping sample was missing, three participants did not give consent for genotyping, and 11 subjects participated twice (only one participation that included all outcome measures was used), resulting in a final data set of 149 subjects (76 women). The mean ± SD body weight was 69 ± 11 kg (range: 46–97 kg).

The exclusion criteria included a history of psychiatric disorders, physical illness, a lifetime history of illicit drug use more than 10 times (with the exception of past cannabis use), illicit drug use within the past 2 months, and illicit drug use during the study, as determined by urine tests that were conducted before the test sessions, as reported in detail elsewhere (52–54). Fifty-five subjects had prior illicit drug experiences (1–8 times), of which 27 subjects had previously used MDMA (1–5 times), 14 subjects had previously used amphetamine or methamphetamine (1–2 times), 11 subjects had previously used cocaine (1–4 times), eight subjects had previously used lysergic acid diethylamide (1–2 times), and 11 subjects had previously used psilocybin (1–4 times).

Study Drug

(±)MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) was administered orally in a single dose of 125 mg prepared as gelatin capsules (25 and 100 mg). Similar amounts of MDMA are found in ecstasy pills (57) and have been used in clinical trials in patients (1, 2). The doses were not adjusted for body weight or sex. The dose per body weight (mean ± SD) was 1.9 ± 0.3 mg/kg (range: 1.3–2.7 mg/kg).

Physiological Effects

Blood pressure, heart rate, and body temperature were assessed repeatedly before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 h after MDMA or placebo administration. Systolic and diastolic blood pressures and heart rate were measured using an automatic oscillometric device (OMRON Healthcare Europe NA, Hoofddorp, Netherlands). The measurements were performed in duplicate at an interval of 1 min and after a resting time of at least 10 min. The averages were calculated for the analysis. Mean arterial pressure (MAP) was calculated as diastolic blood pressure + (systolic blood pressure – diastolic blood pressure)/3. The rate pressure product (RPP) was calculated as systolic blood pressure × heart rate. Core (tympanic) temperature was measured using a Genius 2 ear thermometer (Tyco Healthcare Group LP, Watertown, NY, USA). In two studies (N = 46), the 2-h time point was not used.

Pharmacodynamic Measures

Visual Analog Scales (VASs) were repeatedly used to assess subjective effects over time (58). The VASs included for instance "any drug effect," "good drug effect," and "stimulated." The VASs were presented as 100 mm horizontal lines (0–100%), marked from "not at all" on the left to "extremely" on the right. Subjective effects like "concentration," "appetite," "tired," "want to be hugged," "want to hug," and "talkative" were bidirectional (±50 mm). Not all VAS components were presented in all studies. Exact numbers of subjects per genotype group are reported in **Tables 1–3**. The VASs were applied before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 h after MDMA or placebo administration. In two studies (N = 46), the 2-h time point is missing; additionally, in one study (N = 21), the 2.5-h time point is also missing.

The 60-item Likert-type scale of the short version of the Adjective Mood Rating Scale (AMRS) (59) was administered before and 1.25, 2, and 5 h after MDMA or placebo administration. The AMRS contains subscales for activity, well-being, and anxiety–depression.

Genotyping

Genomic DNA was extracted from whole blood using the QIAamp DNA Blood Mini Kit (Qiagen, Hombrechtikon, Switzerland) and automated QIAcube system. SNP genotyping was performed using commercial TaqMan SNP genotyping assays (LuBio Science, Lucerne, Switzerland). We assayed the following SNPs: DRD2/ankyrin repeat and kinase domain containing 1 (ANKK1) SNPs rs1800497 (assay: C___7486676_10), DRD2 rs6277 (assay: C__11339240_10), and rs1079597 (assay: C___2278884_10), and DAT1 SNPs rs6347 (assay: C___8769902_10) and rs11133767 (assay: C___3024834_10) and rs11564774 (assay: C__25761679_10) and rs460000 (assay: C___3284837_10) and rs463379 (assay: C___3284827_10). We also used the following method to genotype the polymorphisms in DRD4 exon III VNTR, DAT1 3'UTR VNTR rs28363170, and DAT1 Intron 8 (5/6) VNTR rs3836790. Genotypes were determined by polymerase chain reaction (PCR) using 2.5, 1.25, and 1.25 units of HotStarTaq DNA polymerase (QIAGEN Instruments AG, Hombrechtikon, Switzerland), respectively; 1.5 µl PCR Buffer 10x each (15 mM Mg^{2+}; QIAGEN Instruments AG, Hombrechtikon, Switzerland); 0.25, 1, and 1 µl dNTP Mix (40 mM), respectively; and primer set *5'-GCGACTACGTGGTCTACTCG* and *5'-AGGACCCTCATGGCCTTG, 5'-TGTGGTGTAGGGAACG GCCTGAG* and *5'-CTTCCTGGAGGTCACGGCTCAAGG*, and *5'-G CATGTGGATGTGTTCTTGCA* and *5'-TCATCCCAGGGACATCT GCTA* (both 1 µl, both 0.5 µl, and both 0.5 µl, respectively) in a total reaction volume of 15 µl each. The following temperature profile was applied in a T100 thermal cycler (Bio-Rad, Cressier, Switzerland): for DRD4 (Exon III VNTR): initial activation step of 95°C (15 min) and 30 cycles of 98°C (60 s), 67.5°C (60 s), and 72°C (60 s), with final extension at 72°C (5 min); for DAT1 (3'UTR VNTR) rs28363170 and (intron8 5/6 VNTR) rs3836790: initial activation step of 95°C (15 min) and 30 cycles of 98°C (25 s), 95°C (35 s), and 72°C (45 s), with final extension at 72°C (5 min). The sizes of the resulting PCR products were assessed by 3.5% (for DRD4 exon III VNTR) and 2.5% (for DAT1 3'UTR VNTR rs28363170 and Intron 8 VNTR rs3836790) agarose gel electrophoresis. Amplicons of the DRD4 (Exon III VNTR in chromosome 11) of 379 bp were designated as 2 repeats (2R), and amplicons of every additional 48 bp were designated as 2+x times 48 bp variants [up to 9R (with 379 bp + 7 × 48 bp = 715 bp)]. Four and 7-repeat amplicons were the

TABLE 1 | Effects of polymorphisms in the dopamine receptor D2 gene on the maximal response to 125 mg MDMA (mean ± SD (N) and statistics) corrected with MDMA AUC_6 (exclusive plasma concentrations).

DRD2/ANKK1 rs1800497	**AA**	**AG**	**GG**	**F**	**p value**	**p value[a]**	**η^2**
N	2	46	101				
Female, N [%]	1 (50)	30 [65]	45 [45]				
Drug experience, N [%]	2 (100)	17 [37]	36 [36]				
MDMA plasma concentration Cmax, ng/ml	236 ± 76 (2)	239 ± 47 (46)	223 ± 49 (101)	1.71	NS	NS	0.023
MDMA plasma concentration AUC_6, ng*h/ml	964 ± 235 (2)	994 ± 199 (46)	944 ± 205 (101)	0.97	NS	NS	0.013
Visual Analog Scale rating ΔE_{max}							
Any drug effect	84 ± 18 (2)	77 ± 23 (46)	70 ± 28 (101)	0.74	NS	NS	0.008
Good drug effect	94 ± 9 (2)	78 ± 26 (46)	70 ± 30 (101)	1.31	NS	NS	0.016
Bad drug effect	24 ± 35 (2)	21 ± 25 (46)	14 ± 24 (101)	1.14	NS	NS	0.015
Drug liking	96 ± 6 (2)	78 ± 28 (46)	72 ± 29 (101)	1.03	NS	NS	0.013
Stimulated	91 ± 13 (2)	68 ± 32 (46)	59 ± 35 (101)	1.44	NS	NS	0.018
High mood	96 ± 6 (2)	73 ± 30 (46)	66 ± 34 (101)	0.98	NS	NS	0.012
Concentration	28 ± 31 (2)	6.2 ± 14 (46)	9.2 ± 16 (101)	2.09	NS	NS	0.028
Talkative	48 ± 4 (2)	18 ± 20 (46)	22 ± 18 (101)	3.12	0.047*	NS	0.040
Appetite	7.5 ± 9.2 (2)	-5.3 ± 39 (23)	-8.9 ± 27 (47)	0.43	NS	NS	0.012
Tired	24 ± 8 (2)	19 ± 34 (33)	20 ± 32 (74)	0.07	NS	NS	0.001
Fear	7.0 ± 9.9 (2)	7.3 ± 15 (31)	5.9 ± 17 (64)	0.06	NS	NS	0.001
Happy	50 (1)	26 ± 19 (32)	27 ± 19 (73)	0.63	NS	NS	0.011
Want to be hugged	NA (0)	13 ± 18 (23)	13 ± 19 (54)	0.12	NS	NS	0.001
Want to hug	NA (0)	14 ± 17 (23)	13 ± 18 (54)	0.02	NS	NS	0.000
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	21 ± 31 (2)	25 ± 11 (46)	23 ± 13 (101)	0.32	NS	NS	0.004
Diastolic blood pressure, mmHg	13 ± 11 (2)	15 ± 10 (46)	13 ± 9 (101)	0.78	NS	NS	0.010
Mean arterial pressure, mmHg	14 ± 22 (2)	19 ± 10 (46)	16 ± 9 (101)	0.91	NS	NS	0.011
Heat rate beat/min	31 ± 33 (2)	20 ± 15 (46)	16 ± 13 (101)	2.07	NS	NS	0.027
Rate pressure product, mmHg/min	6,343 ± 6,658 (2)	4,967 ± 2,855 (46)	4,203 ± 2,776 (101)	1.26	NS	NS	0.017
Body temperature, °C	0.5 ± 0.1 (2)	0.2 ± 0.4 (46)	0.2 ± 0.5 (101)	0.34	NS	NS	0.005
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	10 ± 8 (2)	2.1 ± 4.2 (46)	2.4 ± 5.3 (101)	2.40	0.09	NS	0.032
High mood	7.5 ± 0.7 (2)	2.2 ± 2.8 (46)	3.0 ± 3.2 (101)	3.49	0.033*	NS	0.046
Fear/depression	-1.5 ± 2.1 (2)	1.2 ± 3.3 (46)	1.2 ± 3.4 (101)	0.63	NS	NS	0.009
DRD2 rs6277	**AA**	**AG**	**GG**	**F**	**p value**	**p value[a]**	**η^2**
N	50	73	26				
Female, N [%]	25 [50]	39 [53]	12 [46]				
Drug experience, N [%]	18 [36]	29 [40]	8 [31]				
MDMA plasma concentration Cmax, ng/ml	225 ± 52 (50)	233 ± 47 (73)	221 ± 47 (26)	0.70	NS	NS	0.009
MDMA plasma concentration AUC_6, ng*h/ml	949 ± 213 (50)	974 ± 203 (73)	939 ± 186 (26)	0.38	NS	NS	0.005
Visual Analog Scale rating ΔE_{max}							
Any drug effect	70 ± 31 (50)	73 ± 25 (73)	77 ± 21 (26)	0.95	NS	NS	0.011
Good drug effect	72 ± 31 (50)	74 ± 26 (73)	71 ± 31 (26)	0.04	NS	NS	0.000
Bad drug effect	11 ± 21 (50)	16 ± 24 (73)	25 ± 30 (26)	3.42	0.036*	NS	0.043
Drug liking	74 ± 30 (50)	74 ± 26 (73)	73 ± 34 (26)	0.01	NS	NS	0.000
Stimulated	57 ± 37 (50)	63 ± 33 (73)	71 ± 32 (26)	1.63	NS	NS	0.020
High mood	67 ± 33 (50)	70 ± 32 (73)	67 ± 36 (26)	0.09	NS	NS	0.001
Concentration	10 ± 16 (50)	6.3 ± 15 (73)	12 ± 18 (26)	1.59	NS	NS	0.021
Talkative	22 ± 18 (50)	20 ± 19 (73)	22 ± 20 (26)	0.25	NS	NS	0.003
Appetite	-17 ± 32 (26)	-0.8 ± 30 (35)	-4.5 ± 25 (11)	2.26	NS	NS	0.061
Tired	23 ± 33 (36)	20 ± 33 (55)	14 ± 29 (18)	0.44	NS	NS	0.008
Fear	4.5 ± 10 (35)	5.7 ± 14 (47)	13 ± 29 (15)	1.64	NS	NS	0.034
Happy	29 ± 18 (32)	26 ± 20 (53)	27 ± 18 (21)	0.30	NS	NS	0.005
Want to be hugged	13 ± 18 (24)	13 ± 19 (38)	12 ± 17 (15)	0.08	NS	NS	0.002
Want to hug	12 ± 17 (24)	14 ± 19 (38)	13 ± 16 (15)	0.01	NS	NS	0.000
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	24 ± 13 (50)	23 ± 13 (73)	24 ± 11 (26)	0.10	NS	NS	0.001
Diastolic blood pressure, mmHg	13 ± 9 (50)	14 ± 8 (73)	14 ± 13 (26)	0.08	NS	NS	0.001
Mean arterial pressure, mmHg	17 ± 10 (50)	17 ± 9 (73)	18 ± 11 (26)	0.16	NS	NS	0.002
Heat rate beat/min	19 ± 14 (50)	16 ± 15 (73)	20 ± 14 (26)	1.57	NS	NS	0.021
Rate pressure product, mmHg/min	4,635 ± 2,630 (50)	4,211 ± 3,111 (73)	4,867 ± 2,541 (26)	0.85	NS	NS	0.011
Body temperature, °C	0.3 ± 0.6 (50)	0.2 ± 0.5 (73)	0.2 ± 0.4 (26)	0.42	NS	NS	0.006
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	2.6 ± 5.7 (50)	2.2 ± 4.9 (73)	2.7 ± 4.5 (26)	0.15	NS	NS	0.002

(Continued)

TABLE 1 | Continued

DRD2/ANKK1 rs1800497	AA	AG	GG	F	p value	p value[a]	η^2
High mood	3.1 ± 3.2 (50)	2.9 ± 3.2 (73)	2.1 ± 3.0 (26)	0.84	NS	NS	0.012
Fear/depression	0.7 ± 3 (50)	1.3 ± 3.1 (73)	1.5 ± 4.5 (26)	0.79	NS	NS	0.011
DRD2 rs1079597	**CC**	**CT**	**TT**	**F**	**p value**	**p value[a]**	**η^2**
N	111	37	1				
Female, N [%]	53 [48]	22 [59]	1 [100]				
Drug experience, N [%]	40 [36]	14 [38]	1 [100]				
MDMA plasma concentration Cmax, ng/ml	226 ± 49 (111)	234 ± 49 (37)	290 (1)	1.19	NS	NS	0.016
MDMA plasma concentration AUC_6, ng*h/ml	949 ± 202 (111)	985 ± 208 (37)	1130 (1)	0.78	NS	NS	0.011
Visual Analog Scale rating ΔE_{max}							
Any drug effect	71 ± 28 (111)	76 ± 21 (37)	96 (1)	0.44	NS	NS	0.005
Good drug effect	71 ± 30 (111)	76 ± 25 (37)	100 (1)	0.44	NS	NS	0.006
Bad drug effect	13 ± 24 (111)	25 ± 26 (37)	0 (1)	3.09	0.049*	NS	0.039
Drug liking	73 ± 29 (111)	77 ± 28 (37)	100 (1)	0.40	NS	NS	0.005
Stimulated	59 ± 35 (111)	71 ± 31 (37)	100 (1)	1.64	NS	NS	0.020
High mood	68 ± 33 (111)	70 ± 32 (37)	100 (1)	0.28	NS	NS	0.004
Concentration	8.9 ± 16 (111)	6.3 ± 15 (37)	50 (1)	3.92	0.022*	NS	0.051
Talkative	22 ± 18 (111)	19 ± 21 (37)	50 (1)	1.58	NS	NS	0.020
Appetite	-11 ± 29 (53)	2.4 ± 35 (18)	1.0 (1)	1.35	NS	NS	0.037
Tired	21 ± 32 (80)	18 ± 34 (28)	30 (1)	0.14	NS	NS	0.002
Fear	5.5 ± 16 (73)	9.5 ± 17 (23)	0 (1)	0.61	NS	NS	0.013
Happy	27 ± 19 (78)	26 ± 19 (27)	50 (1)	0.62	NS	NS	0.011
Want to be hugged	13 ± 18 (58)	14 ± 19 (19)	NA (0)	0.01	NS	NS	0.000
Want to hug	13 ± 18 (58)	15 ± 18 (19)	NA (0)	0.03	NS	NS	0.000
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	23 ± 13 (111)	26 ± 11 (37)	43 (1)	1.52	NS	NS	0.019
Diastolic blood pressure, mmHg	13 ± 9 (111)	15 ± 11 (37)	20 (1)	0.65	NS	NS	0.008
Mean arterial pressure, mmHg	16 ± 9 (111)	19 ± 10 (37)	29 (1)	1.33	NS	NS	0.017
Heat rate beat/min	16 ± 14 (111)	20 ± 14 (37)	54 (1)	3.89	0.023*	NS	0.050
Rate pressure product, mmHg/min	4,240 ± 2,838 (111)	4,972 ± 2,700 (37)	11,050 (1)	3.24	0.042*	NS	0.041
Body temperature, °C	0.2 ± 0.5 (111)	0.3 ± 0.4 (37)	0.6 (1)	0.65	NS	NS	0.009
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	2.4 ± 5.3 (111)	2.0 ± 3.9 (37)	16 (1)	3.74	0.026*	NS	0.049
High mood	3 ± 3.2 (111)	2.3 ± 2.8 (37)	8.0 (1)	1.92	NS	NS	0.026
Fear/depression	1.1 ± 3.2 (111)	1.2 ± 3.7 (37)	0 (1)	0.07	NS	NS	0.001

*N, number of subjects; SD, standard deviation; NS, not significant; Δ, values are change scores from placebo; [a]p value additionally corrected for multiple comparisons according to the Nyholt method; η^2, eta square; *, uncorrected p < 0.05.*

most common forms. Complete genotype and allele distributions are depicted in **Supplementary Table S1**. For the analysis, groups were made with cumulative ≤8 repeats or cumulative >8 repeats in both alleles. Amplicons of the DAT1 (3'UTR VNTR) rs28363170 of 448 bp were designated as 9 repeats (9R), and amplicons of 488 bp were designated as 10R. Individuals possessing other repeats were excluded from the analysis. Amplicons of the DAT1 (intron 8 5/6 VNTR) rs3836790 of 295 bp were designated as 5 repeats (5R), and amplicons of 325 bp were designated as 6 repeats (6R). The pairwise linkage disequilibrium (LD) and relative physical location of the determined SNPs on chromosome 11 (DRD2) and 5 (DAT1) are shown in Supplementary Figure 1. The tested genetic variants were consistent with Hardy–Weinberg equilibrium ($p > 0.05$).

Statistical Analysis

The statistical analyses were performed using Statistica 12 software (StatSoft, Tulsa, OK, USA). For repeatedly measured data, peak effects (E_{max}) and areas under the effect-time curve (AUEC) from 0- to 6-h values were determined for MDMA and placebo. Differences in E_{max} (Δ; MDMA-placebo) were then analyzed using one-way analysis of variance (ANOVA), with genotype as the between-group factor. The level of significance was set at $p < 0.05$. The Nyholt correction method was used to account for multiple comparisons and displayed separately in all tables (60). We thereby corrected for 17 subjective effect ratings (VAS+AMRS), and six vital parameters. In addition, this was then corrected for each of the 11 polymorphisms tested, resulting in (17 + 6) × 11 = 253 variables and an effective number of independent variables (V_{eff}) of 183.6 according to Nyholt. Consequently, this led to a corrected significance threshold of $p < 0.00027$ to keep Type I error rate at 5%. To account for differences in plasma concentrations of MDMA that were caused by differences in body weight, dosing, or metabolizing enzymes (17, 18), the area under the MDMA plasma concentration–time curve from 0 to 6 h (AUC) was included as a covariate in the ANOVAs, and we report the corrected statistics. Additionally, modulatory effects of sex were explored by adding sex as a between-subjects factor in the ANOVAs (sex × genotype). E_{max} values were obtained directly from the observed data. AUC and AUEC values were calculated using the linear-log trapezoidal method in Phoenix WinNonlin 6.4 (Certara, Princeton, NJ, USA). The primary analysis was performed using an additive genotype model approach for SNPs. Recessive or dominant model analysis

TABLE 2 | Effects of polymorphisms in the dopamine transporter 1 gene on the maximal response to 125 mg MDMA (mean ± SD (N) and statistics) corrected with MDMA AUC_6 (exclusive plasma concentrations).

DAT1 3'-UTR rs28363170	**99**	**910**	**1010**	**F**	**p value**	**p value[a]**	**η^2**
N	8	56	79				
Female, N [%]	2 [25]	29 [52]	41 [52]				
Drug experience, N [%]	4 [50]	18 [32]	31 [39]				
MDMA plasma concentration Cmax, ng/ml	221 ± 44 (8)	227 ± 46 (56)	230 ± 50 (79)	0.14	NS	NS	0.002
MDMA plasma concentration AUC_6, ng*h/ml	939 ± 183 (8)	958 ± 180 (56)	961 ± 214 (79)	0.04	NS	NS	0.001
Visual Analog Scale rating ΔE_{max}							
Any drug effect	78 ± 20 (8)	73 ± 26 (56)	71 ± 28 (79)	0.48	NS	NS	0.006
Good drug effect	84 ± 21 (8)	73 ± 28 (56)	71 ± 30 (79)	0.97	NS	NS	0.013
Bad drug effect	11 ± 21 (8)	15 ± 29 (56)	16 ± 22 (79)	0.14	NS	NS	0.002
Drug liking	83 ± 22 (8)	77 ± 26 (56)	70 ± 31 (79)	1.26	NS	NS	0.017
Stimulated	63 ± 35 (8)	60 ± 35 (56)	63 ± 35 (79)	0.09	NS	NS	0.001
High mood	79 ± 32 (8)	68 ± 34 (56)	67 ± 33 (79)	0.57	NS	NS	0.008
Concentration	14 ± 22 (8)	7.3 ± 16 (56)	9.3 ± 16 (79)	0.76	NS	NS	0.011
Talkative	23 ± 16 (8)	19 ± 18 (56)	22 ± 19 (79)	0.56	NS	NS	0.008
Appetite	-20 ± 25 (7)	-2.6 ± 37 (28)	-7 ± 26 (35)	1.14	NS	NS	0.032
Tired	6.9 ± 37 (7)	17 ± 31 (44)	25 ± 33 (53)	1.38	NS	NS	0.026
Fear	6.3 ± 21 (7)	4.1 ± 9.5 (33)	8 ± 19 (55)	0.59	NS	NS	0.013
Happy	15 ± 16 (3)	27 ± 20 (40)	27 ± 18 (59)	0.37	NS	NS	0.007
Want to be hugged	0 (1)	16 ± 20 (28)	10 ± 16 (44)	1.16	NS	NS	0.030
Want to hug	0 (1)	16 ± 19 (28)	11 ± 16 (44)	1.01	NS	NS	0.027
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	27 ± 15 (8)	25 ± 11 (56)	22 ± 14 (79)	1.06	NS	NS	0.014
Diastolic blood pressure, mmHg	21 ± 18 (8)	14 ± 8 (56)	12 ± 9 (79)	3.84	0.024*	NS	0.049
Mean arterial pressure, mmHg	25 ± 14 (8)	18 ± 8 (56)	16 ± 10 (79)	3.79	0.025*	NS	0.048
Heat rate beat/min	16 ± 8 (8)	18 ± 15 (56)	16 ± 15 (79)	0.28	NS	NS	0.004
Rate pressure product, mmHg/min	4,623 ± 2,214 (8)	4,684 ± 2,835 (56)	4,194 ± 2,970 (79)	0.54	NS	NS	0.007
Body temperature, °C	0 ± 0.3 (8)	0.3 ± 0.5 (56)	0.2 ± 0.5 (79)	1.34	NS	NS	0.019
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	4.0 ± 5.2 (8)	2.0 ± 4.9 (56)	2.3 ± 5.2 (79)	0.53	NS	NS	0.008
High mood	2.6 ± 1.5 (8)	3.0 ± 3.2 (56)	2.7 ± 3.3 (79)	0.16	NS	NS	0.002
Fear/depression	0.5 ± 2 (8)	1.5 ± 3.6 (56)	1 ± 3 (79)	0.64	NS	NS	0.009
DAT1 Intron 8 rs3836790	**55**	**56**	**66**	**F**	**p value**	**p value[a]**	**η^2**
N	7	54	85				
Female, N [%]	3 [43]	25 [46]	46 [54]				
Drug experience, N [%]	4 [57]	21 [39]	29 [34]				
MDMA plasma concentration Cmax, ng/ml	218 ± 43 (7)	225 ± 54 (54)	231 ± 45 (85)	0.48	NS	NS	0.007
MDMA plasma concentration AUC_6, ng*h/ml	894 ± 201 (7)	945 ± 211 (54)	972 ± 196 (85)	0.65	NS	NS	0.009
Visual Analog Scale rating ΔE_{max}							
Any drug effect	66 ± 20 (7)	69 ± 29 (54)	75 ± 26 (85)	0.59	NS	NS	0.007
Good drug effect	69 ± 26 (7)	72 ± 30 (54)	74 ± 28 (85)	0.05	NS	NS	0.001
Bad drug effect	-0.7 ± 19 (7)	18 ± 29 (54)	16 ± 21 (85)	1.57	NS	NS	0.020
Drug liking	79 ± 20 (7)	73 ± 29 (54)	74 ± 30 (85)	0.24	NS	NS	0.003
Stimulated	58 ± 33 (7)	58 ± 35 (54)	66 ± 34 (85)	0.70	NS	NS	0.009
High mood	65 ± 27 (7)	66 ± 36 (54)	71 ± 31 (85)	0.19	NS	NS	0.003
Concentration	-0.6 ± 5 (7)	9.2 ± 18 (54)	8.5 ± 15 (85)	1.18	NS	NS	0.016
Talkative	15 ± 15 (7)	20 ± 19 (54)	22 ± 19 (85)	0.37	NS	NS	0.005
Appetite	-21 ± 29 (3)	-9.8 ± 34 (25)	-4.9 ± 30 (43)	0.49	NS	NS	0.014
Tired	-10 ± 28 (5)	20 ± 33 (41)	22 ± 31 (61)	1.82	NS	NS	0.032
Fear	1.7 ± 2.9 (3)	4.7 ± 14 (35)	7.7 ± 18 (58)	0.48	NS	NS	0.010
Happy	20 ± 16 (4)	26 ± 19 (42)	29 ± 19 (57)	0.28	NS	NS	0.005
Want to be hugged	9.8 ± 20 (4)	13 ± 19 (29)	14 ± 18 (42)	0.05	NS	NS	0.001
Want to hug	8.5 ± 17 (4)	14 ± 19 (29)	14 ± 18 (42)	0.06	NS	NS	0.001
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	31 ± 7 (7)	24 ± 12 (54)	23 ± 14 (85)	2.00	NS	NS	0.026
Diastolic blood pressure, mmHg	18 ± 6 (7)	15 ± 11 (54)	12 ± 8 (85)	2.99	0.05	NS	0.038
Mean arterial pressure, mmHg	23 ± 6 (7)	18 ± 10 (54)	16 ± 10 (85)	3.67	0.028*	NS	0.046
Heat rate beat/min	16 ± 5 (7)	19 ± 15 (54)	17 ± 14 (85)	0.38	NS	NS	0.005
Rate pressure product, mmHg/min	4,394 ± 1,421 (7)	4,878 ± 2,775 (54)	4,264 ± 2,999 (85)	0.96	NS	NS	0.013
Body temperature, °C	0.6 ± 0.6 (7)	0.3 ± 0.5 (54)	0.2 ± 0.5 (85)	2.59	0.08	NS	0.035
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	1.7 ± 3.1 (7)	2.2 ± 5.9 (54)	2.4 ± 4.7 (85)	0.08	NS	NS	0.001
High mood	2.3 ± 1.9 (7)	2.7 ± 3.3 (54)	3.0 ± 3.2 (85)	0.29	NS	NS	0.004
Hear/depression	-1.1 ± 2.8 (7)	1.4 ± 3.2 (54)	1.2 ± 3.5 (85)	1.80	NS	NS	0.025

(Continued)

TABLE 2 | Continued

DAT1 rs6347	CC	CT	TT	F	p value	p value[a]	η^2
N	12	60	77				
Female, N [%]	6 [50]	29 [48]	41 [53]				
Drug experience, N [%]	5 [42]	23 [38]	27 [35]				
MDMA plasma concentration Cmax, ng/ml	225 ± 46 (12)	224 ± 50 (60)	232 ± 48 (77)	0.45	NS	NS	0.006
MDMA plasma concentration AUC_6, ng*h/ml	933 ± 221 (12)	947 ± 192 (60)	973 ± 210 (77)	0.39	NS	NS	0.005
Visual Analog Scale rating ΔE_{max}							
Any drug effect	68 ± 24 (12)	70 ± 29 (60)	76 ± 25 (77)	0.73	NS	NS	0.008
Good drug effect	70 ± 26 (12)	71 ± 30 (60)	74 ± 28 (77)	0.12	NS	NS	0.002
Bad drug effect	3.9 ± 18 (12)	17 ± 29 (60)	17 ± 21 (77)	1.47	NS	NS	0.019
Drug liking	77 ± 23 (12)	72 ± 30 (60)	75 ± 29 (77)	0.16	NS	NS	0.002
Stimulated	65 ± 29 (12)	56 ± 36 (60)	67 ± 33 (77)	1.37	NS	NS	0.017
High mood	68 ± 28 (12)	66 ± 36 (60)	71 ± 31 (77)	0.16	NS	NS	0.002
Concentration	3.7 ± 10 (12)	8.4 ± 18 (60)	9.4 ± 15 (77)	0.69	NS	NS	0.009
Talkative	22 ± 15 (12)	19 ± 20 (60)	22 ± 18 (77)	0.29	NS	NS	0.004
Appetite	-4.1 ± 25 (7)	-13 ± 33 (27)	-3.8 ± 30 (38)	0.71	NS	NS	0.020
Tired	12 ± 36 (10)	20 ± 31 (42)	22 ± 33 (57)	0.28	NS	NS	0.005
Fear	1.0 ± 1.9 (7)	4.6 ± 13 (40)	8.5 ± 19 (50)	1.09	NS	NS	0.023
Happy	25 ± 15 (7)	25 ± 20 (45)	29 ± 19 (54)	0.36	NS	NS	0.007
Want to be hugged	11 ± 17 (5)	11 ± 18 (33)	15 ± 19 (39)	0.30	NS	NS	0.008
Want to hug	10 ± 15 (5)	10 ± 17 (33)	16 ± 18 (39)	0.70	NS	NS	0.017
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	29 ± 8 (12)	24 ± 13 (60)	23 ± 13 (77)	1.87	NS	NS	0.024
Diastolic blood pressure, mmHg	17 ± 7 (12)	14 ± 11 (60)	12 ± 8 (77)	2.19	NS	NS	0.027
Mean arterial pressure, mmHg	22 ± 6 (12)	18 ± 10 (60)	16 ± 10 (77)	2.87	0.06	NS	0.035
Heat rate beat/min	16 ± 12 (12)	17 ± 15 (60)	18 ± 14 (77)	0.03	NS	NS	0.000
Rate pressure product, mmHg/min	4,592 ± 2,500 (12)	4,550 ± 2,840 (60)	4,384 ± 2,950 (77)	0.14	NS	NS	0.002
Body temperature, °C	0.4 ± 0.6 (12)	0.2 ± 0.5 (60)	0.2 ± 0.5 (77)	1.13	NS	NS	0.015
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	3.3 ± 5.1 (12)	2.3 ± 5.7 (60)	2.4 ± 4.6 (77)	0.23	NS	NS	0.003
High mood	3.7 ± 2.6 (12)	2.6 ± 3.2 (60)	2.9 ± 3.2 (77)	0.66	NS	NS	0.009
Fear/depression	-0.8 ± 2 (12)	1.2 ± 3.3 (60)	1.4 ± 3.4 (77)	2.28	NS	NS	0.030
DAT1 rs11133767	**CC**	**CT**	**TT**	**F**	**p value**	**p value[a]**	**η^2**
N	62	66	20				
Female, N [%]	33 [53]	35 [53]	7 [35]				
Drug experience, N [%]	22 [35]	18 [27]	14 [70]				
MDMA plasma concentration Cmax, ng/ml	230 ± 48 (62)	230 ± 48 (66)	213 ± 50 (20)	1.05	NS	NS	0.014
MDMA plasma concentration AUC_6, ng*h/ml	965 ± 210 (62)	977 ± 200 (66)	876 ± 179 (20)	1.98	NS	NS	0.027
Visual Analog Scale rating ΔE_{max}							
Any drug effect	75 ± 25 (62)	69 ± 28 (66)	74 ± 23 (20)	1.70	NS	NS	0.019
Good drug effect	74 ± 28 (62)	70 ± 30 (66)	77 ± 26 (20)	1.38	NS	NS	0.018
Bad drug effect	18 ± 23 (62)	14 ± 25 (66)	16 ± 29 (20)	0.73	NS	NS	0.009
Drug liking	74 ± 31 (62)	72 ± 29 (66)	82 ± 23 (20)	1.72	NS	NS	0.022
Stimulated	68 ± 32 (62)	57 ± 36 (66)	63 ± 35 (20)	2.37	0.10	NS	0.029
High mood	71 ± 32 (62)	65 ± 34 (66)	72 ± 34 (20)	1.40	NS	NS	0.018
Concentration	9.5 ± 16 (62)	7.8 ± 16 (66)	8.6 ± 16 (20)	0.19	NS	NS	0.003
Talkative	23 ± 19 (62)	19 ± 19 (66)	21 ± 17 (20)	0.61	NS	NS	0.008
Appetite	-2.9 ± 29 (32)	-8.6 ± 30 (27)	-15 ± 35 (13)	1.21	NS	NS	0.034
Tired	25 ± 34 (45)	19 ± 28 (47)	10 ± 37 (17)	1.13	NS	NS	0.020
Fear	8.9 ± 20 (44)	1.8 ± 4.9 (37)	11 ± 20 (15)	2.57	0.08	NS	0.053
Happy	27 ± 19 (42)	26 ± 19 (52)	30 ± 17 (11)	0.87	NS	NS	0.016
Want to be hugged	10 ± 16 (30)	15 ± 19 (39)	14 ± 22 (7)	0.44	NS	NS	0.011
Want to hug	11 ± 16 (30)	15 ± 18 (39)	14 ± 22 (7)	0.38	NS	NS	0.010
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	22 ± 13 (62)	25 ± 13 (66)	23 ± 12 (20)	1.43	NS	NS	0.018
Diastolic blood pressure, mmHg	12 ± 8 (62)	14 ± 9 (66)	15 ± 12 (20)	1.83	NS	NS	0.023
Mean arterial pressure, mmHg	16 ± 9 (62)	18 ± 9 (66)	19 ± 11 (20)	1.86	NS	NS	0.023
Heat rate beat/min	17 ± 15 (62)	18 ± 15 (66)	18 ± 12 (20)	0.05	NS	NS	0.001
Rate pressure product, mmHg/min	4,337 ± 3,024 (62)	4,600 ± 2,817 (66)	4,551 ± 2,573 (20)	0.23	NS	NS	0.003
Body temperature, °C	0.2 ± 0.5 (62)	0.3 ± 0.5 (66)	0.3 ± 0.5 (20)	0.72	NS	NS	0.010
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	3.2 ± 4.9 (62)	2 ± 5.7 (66)	1.4 ± 2.9 (20)	1.23	NS	NS	0.017
High mood	3.1 ± 3.3 (62)	2.7 ± 3.3 (66)	2.4 ± 2.1 (20)	0.42	NS	NS	0.006
Fear/depression	1.0 ± 3.6 (62)	1.4 ± 3.3 (66)	0.6 ± 2 (20)	0.42	NS	NS	0.006

(Continued)

TABLE 2 | Continued

DAT1 rs11564774	CC	CG	GG	F	p value	p value[a]	η^2
N	81	58	10				
Female, N [%]	43 [53]	32 [55]	1 [10]				
Drug experience, N [%]	31 [38]	17 [29]	7 [70]				
MDMA plasma concentration Cmax, ng/ml	230 ± 49 (81)	230 ± 49 (58)	199 ± 35 (10)	1.96	NS	NS	0.026
MDMA plasma concentration AUC_6, ng*h/ml	967 ± 211 (81)	967 ± 196 (58)	851 ± 155 (10)	1.55	NS	NS	0.021
Visual Analog Scale rating ΔE_{max}							
Any drug effect	72 ± 27 (81)	73 ± 27 (58)	74 ± 23 (10)	0.60	NS	NS	0.007
Good drug effect	71 ± 29 (81)	75 ± 28 (58)	75 ± 27 (10)	0.59	NS	NS	0.007
Bad drug effect	17 ± 22 (81)	16 ± 26 (58)	13 ± 36 (10)	0.03	NS	NS	0.000
Drug liking	71 ± 31 (81)	77 ± 27 (58)	78 ± 21 (10)	0.95	NS	NS	0.012
Stimulated	64 ± 34 (81)	62 ± 36 (58)	51 ± 30 (10)	0.29	NS	NS	0.004
High mood	69 ± 32 (81)	68 ± 35 (58)	73 ± 29 (10)	0.40	NS	NS	0.005
Concentration	9.0 ± 15 (81)	7.4 ± 16 (58)	11 ± 20 (10)	0.29	NS	NS	0.004
Talkative	23 ± 19 (81)	19 ± 19 (58)	20 ± 11 (10)	0.55	NS	NS	0.007
Appetite	-4.8 ± 28 (36)	-6.4 ± 34 (29)	-24 ± 27 (7)	1.51	NS	NS	0.041
Tired	24 ± 33 (54)	16 ± 31 (46)	12 ± 29 (9)	1.00	NS	NS	0.018
Fear	8 ± 19 (55)	2.5 ± 5.8 (35)	13 ± 25 (7)	1.86	NS	NS	0.038
Happy	27 ± 18 (60)	28 ± 20 (41)	21 ± 14 (5)	0.05	NS	NS	0.001
Want to be hugged	10 ± 16 (45)	19 ± 21 (29)	0 ± 0 (3)	2.36	NS	NS	0.056
Want to hug	11 ± 16 (45)	19 ± 20 (29)	0 ± 0 (3)	2.26	NS	NS	0.053
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	23 ± 14 (81)	25 ± 11 (58)	24 ± 12 (10)	0.49	NS	NS	0.006
Diastolic blood pressure, mmHg	13 ± 9 (81)	14 ± 8 (58)	18 ± 17 (10)	2.97	0.05	NS	0.037
Mean arterial pressure, mmHg	16 ± 10 (81)	18 ± 8 (58)	22 ± 13 (10)	2.90	0.06	NS	0.036
Heat rate beat/min	16 ± 15 (81)	19 ± 15 (58)	16 ± 7 (10)	0.66	NS	NS	0.009
Rate pressure product, mmHg/min	4,219 ± 2,944 (81)	4,902 ± 2,877 (58)	3,963 ± 1,624 (10)	1.03	NS	NS	0.013
Body temperature, °C	0.2 ± 0.5 (81)	0.3 ± 0.4 (58)	0.3 ± 0.6 (10)	0.73	NS	NS	0.010
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	2.5 ± 5.2 (81)	2.4 ± 5.3 (58)	2.0 ± 2.7 (10)	0.02	NS	NS	0.000
High mood	2.8 ± 3.3 (81)	3.0 ± 3.2 (58)	2.2 ± 1.3 (10)	0.26	NS	NS	0.004
Fear/depression	0.9 ± 3 (81)	1.4 ± 3.7 (58)	1.2 ± 1.5 (10)	0.46	NS	NS	0.006
DAT1 rs460000	**GG**	**GT**	**TT**	**F**	**p value**	**p value[a]**	**η^2**
N	94	48	7				
Female, N [%]	52 [55]	22 [46]	2 [29]				
Drug experience, N [%]	33 [35]	20 [42]	2 [29]				
MDMA plasma concentration Cmax, ng/ml	232 ± 50 (94)	221 ± 47 (48)	221 ± 37 (7)	0.98	NS	NS	0.013
MDMA plasma concentration AUC_6, ng*h/ml	971 ± 200 (94)	937 ± 214 (48)	958 ± 185 (7)	0.46	NS	NS	0.006
Visual Analog Scale rating ΔE_{max}							
Any drug effect	73 ± 26 (94)	71 ± 28 (48)	72 ± 20 (7)	0.01	NS	NS	0.000
Good drug effect	75 ± 28 (94)	69 ± 31 (48)	67 ± 26 (7)	0.68	NS	NS	0.009
Bad drug effect	18 ± 26 (94)	14 ± 21 (48)	9.1 ± 17 (7)	0.57	NS	NS	0.007
Drug liking	77 ± 27 (94)	69 ± 33 (48)	65 ± 27 (7)	1.27	NS	NS	0.016
Stimulated	61 ± 35 (94)	66 ± 33 (48)	57 ± 37 (7)	0.71	NS	NS	0.009
High mood	70 ± 33 (94)	67 ± 32 (48)	64 ± 33 (7)	0.14	NS	NS	0.002
Concentration	9.1 ± 17 (94)	7.9 ± 15 (48)	5.4 ± 11 (7)	0.23	NS	NS	0.003
Talkative	23 ± 19 (94)	18 ± 18 (48)	17 ± 20 (7)	0.86	NS	NS	0.011
Appetite	-6.8 ± 33 (53)	-6.7 ± 26 (15)	-15 ± 16 (4)	0.11	NS	NS	0.003
Tired	19 ± 32 (72)	22 ± 34 (32)	19 ± 23 (5)	0.23	NS	NS	0.004
Fear	6.4 ± 18 (66)	5 ± 9.5 (27)	14 ± 10 (4)	0.56	NS	NS	0.012
Happy	28 ± 19 (65)	25 ± 19 (38)	24 ± 25 (3)	0.32	NS	NS	0.006
Want to be hugged	16 ± 20 (41)	8.6 ± 15 (33)	20 ± 26 (3)	1.85	NS	NS	0.044
Want to hug	16 ± 19 (41)	8.8 ± 14 (33)	22 ± 26 (3)	2.12	NS	NS	0.050
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	23 ± 13 (94)	24 ± 13 (48)	26 ± 15 (7)	0.35	NS	NS	0.005
Diastolic blood pressure, mmHg	14 ± 10 (94)	13 ± 9 (48)	12 ± 6 (7)	0.16	NS	NS	0.002
Mean arterial pressure, mmHg	17 ± 10 (94)	17 ± 9 (48)	16 ± 7 (7)	0.11	NS	NS	0.001
Heat rate beat/min	17 ± 14 (94)	17 ± 13 (48)	22 ± 21 (7)	0.32	NS	NS	0.004
Rate pressure product, mmHg/min	4,500 ± 2,891 (94)	4,239 ± 2,512 (48)	5,607 ± 4,506 (7)	0.66	NS	NS	0.009
Body temperature, °C	0.2 ± 0.5 (94)	0.3 ± 0.5 (48)	0.2 ± 0.6 (7)	0.84	NS	NS	0.011
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	2.4 ± 5.7 (94)	2.1 ± 4.0 (48)	4.0 ± 2.4 (7)	0.42	NS	NS	0.006
High mood	3 ± 3.1 (94)	2.5 ± 3.3 (48)	3.7 ± 3.5 (7)	0.63	NS	NS	0.009
Fear/depression	1.2 ± 3.2 (94)	1.4 ± 3.6 (48)	-1.4 ± 3.6 (7)	2.25	NS	NS	0.030

(Continued)

TABLE 2 | Continued

DAT1 rs463379	CC	CG	GG	F	p value	p value[a]	η^2
N	7	47	93				
Female, N [%]	2 [29]	21 [45]	51 [55]				
Drug experience, N [%]	2 [29]	20 [43]	32 [34]				
MDMA plasma concentration Cmax, ng/ml	221 ± 37 (7)	221 ± 47 (47)	232 ± 50 (93)	0.86	NS	NS	0.012
MDMA plasma concentration AUC_6, ng*h/ml	958 ± 185 (7)	934 ± 215 (47)	970 ± 200 (93)	0.49	NS	NS	0.007
Visual Analog Scale rating ΔE_{max}							
Any drug effect	72 ± 20 (7)	71 ± 28 (47)	73 ± 26 (93)	0.00	NS	NS	0.000
Good drug effect	67 ± 26 (7)	69 ± 31 (47)	75 ± 28 (93)	0.60	NS	NS	0.008
Bad drug effect	9.1 ± 17 (7)	13 ± 21 (47)	18 ± 27 (93)	0.62	NS	NS	0.008
Drug liking	65 ± 27 (7)	69 ± 33 (47)	77 ± 27 (93)	1.19	NS	NS	0.016
Stimulated	57 ± 37 (7)	65 ± 33 (47)	61 ± 35 (93)	0.68	NS	NS	0.009
High mood	64 ± 33 (7)	67 ± 32 (47)	70 ± 33 (93)	0.10	NS	NS	0.001
Concentration	5.4 ± 11 (7)	8.1 ± 15 (47)	9.2 ± 17 (93)	0.23	NS	NS	0.003
Talkative	17 ± 20 (7)	19 ± 18 (47)	23 ± 19 (93)	0.64	NS	NS	0.009
Appetite	-15 ± 16 (4)	-6.7 ± 26 (15)	-6.8 ± 33 (53)	0.11	NS	NS	0.003
Tired	19 ± 23 (5)	22 ± 34 (32)	19 ± 32 (72)	0.23	NS	NS	0.004
Fear	14 ± 10 (4)	5 ± 9.5 (27)	6.4 ± 18 (66)	0.56	NS	NS	0.012
Happy	24 ± 25 (3)	25 ± 19 (37)	28 ± 18 (64)	0.23	NS	NS	0.004
Want to be hugged	20 ± 26 (3)	7.7 ± 14 (32)	15 ± 19 (40)	2.02	NS	NS	0.050
Want to hug	22 ± 26 (3)	8.1 ± 14 (32)	15 ± 19 (40)	2.22	NS	NS	0.054
Vital signs parameters ΔE_{max}							
Systolic blood pressure, mmHg	26 ± 15 (7)	24 ± 14 (47)	23 ± 13 (93)	0.27	NS	NS	0.004
Diastolic blood pressure, mmHg	12 ± 6 (7)	13 ± 9 (47)	14 ± 10 (93)	0.15	NS	NS	0.002
Mean arterial pressure, mmHg	16 ± 7 (7)	17 ± 9 (47)	17 ± 10 (93)	0.09	NS	NS	0.001
Heat rate beat/min	22 ± 21 (7)	17 ± 13 (47)	17 ± 14 (93)	0.30	NS	NS	0.004
Rate pressure product, mmHg/min	5,607 ± 4,506 (7)	4,245 ± 2,539 (47)	4,514 ± 2,903 (93)	0.64	NS	NS	0.009
Body temperature, °C	0.2 ± 0.6 (7)	0.3 ± 0.5 (47)	0.2 ± 0.5 (93)	0.67	NS	NS	0.009
Adjective Mood Rating Scale rating ΔE_{max}							
Activity	4.0 ± 2.4 (7)	2.1 ± 4.1 (47)	2.4 ± 5.7 (93)	0.41	NS	NS	0.006
High mood	3.7 ± 3.5 (7)	2.5 ± 3.3 (47)	2.9 ± 3.1 (93)	0.57	NS	NS	0.008
Fear/depression	-1.4 ± 3.6 (7)	1.4 ± 3.6 (47)	1.2 ± 3.2 (93)	2.27	NS	NS	0.031

*N, number of subjects; SD, standard deviation; NS, not significant; Δ, values are change scores from placebo; [a]p value additionally corrected for multiple comparisons according to the Nyholt method; η^2, eta square; *, uncorrected p < 0.05.*

was also performed, the results of which are reported only when the additive model was initially significant.

RESULTS

MDMA significantly altered all tested VAS and AMRS E_{max} values. Subjects did not significantly differ in MDMA plasma concentration or previous drug experience across genotype groups, with the exception of DAT1 rs11133767. Participants carrying two T-alleles showed disproportionately more illicit drug experiences than carriers of the C-allele (70% vs. 31%, respectively; $\chi^2 = 11.2$, $p < 0.001$).

The influence of polymorphisms within genes coding for the DRD2, DAT1, and DRD4 on the maximal acute subjective and autonomic effects of MDMA is shown in **Tables 1–3**, respectively. **Supplementary Table S2** shows the data for the total response to MDMA over time (AUEC). **Supplementary Tables S3** and **S4** show the uncorrected statistics for E_{max} and AUEC, respectively. Homozygous A-allele carriers of the DRD2 rs1800497 showed a higher score in VASs "talkative" ($F_{1,147} = 4.23$, $p < 0.05$) and in AMRSs "activity" and "high mood" ($F_{1,147} = 4.62$, $p < 0.05$ and $F_{1,147} = 4.50$, $p < 0.05$, respectively) compared to carriers of the G-allele. Subjects with two 9R-alleles of the DAT1 rs28363170 had a higher MDMA-induced increase in diastolic blood pressure and MAP compared to subjects with a 10R-allele ($F_{1,141} = 7.12$, $p < 0.01$ and $F_{1,141} = 6.56$, $p < 0.05$, respectively). Regarding the DAT1 rs3836790, MDMA produced a higher increase in MAP in individuals homozygous for the 5R-allele compared to 6R-allele carriers ($F_{1,144} = 4.31$, $p < 0.05$).

Nyholt correction for multiple comparisons yielded statistics indicating that the genetic polymorphisms had no significant effect on the subjective and autonomic parameters. Sex did not significantly modulate the results.

DISCUSSION

The current study expands previous research on whether the acute effects of MDMA are modulated by common genetic polymorphisms in pharmacological targets of MDMA. So far, the focus lied on the role of the NE and 5-HT system genetics in the acute effects of MDMA (22, 23). This is the first study to concentrate on a selection of genetic polymorphisms within the human DA system (namely, D_2, D_4, and DAT).

Action on the DA system is thought to be crucial for the effects of most psychostimulant substances (6, 24, 61), and pharmacogenetic studies demonstrated that different phenotypes are affected by various DA genotypes. As for MDMA, however, none of the herein investigated genetic polymorphisms significantly altered the acute effects after consideration of Type I error correction.

TABLE 3 | Effects of the variable-number tandem repeat polymorphism in the dopamine receptor D4 gene on the maximal response to 125 mg MDMA (mean ± SD (N) and statistics) corrected with MDMA AUC_6 (exclusive plasma concentrations).

DRD4 VNTR	≤8 Repeats	>8 Repeats	F	p value	p value[a]	η^2
N	87	59				
Female, N [%]	44 [51]	31 [53]				
Drug experience, N [%]	31 [36]	22 [37]				
MDMA plasma concentration Cmax, ng/ml	229 ± 44 (87)	226 ± 55 (59)	0.16	NS	NS	0.001
MDMA plasma concentration AUC_6, ng*h/ml	965 ± 189 (87)	948 ± 221 (59)	0.25	NS	NS	0.002
Visual Analog Scale rating ΔE_{max}						
Any drug effect	74 ± 26 (87)	71 ± 26 (59)	0.35	NS	NS	0.002
Good drug effect	73 ± 30 (87)	73 ± 26 (59)	0.01	NS	NS	0.000
Bad drug effect	17 ± 23 (87)	15 ± 27 (59)	0.08	NS	NS	0.001
Drug liking	74 ± 31 (87)	75 ± 25 (59)	0.12	NS	NS	0.001
Stimulated	63 ± 35 (87)	63 ± 34 (59)	0.07	NS	NS	0.000
High mood	68 ± 34 (87)	71 ± 31 (59)	0.51	NS	NS	0.003
Concentration	8.2 ± 17 (87)	9.0 ± 15 (59)	0.09	NS	NS	0.001
Talkative	20 ± 19 (87)	23 ± 19 (59)	1.27	NS	NS	0.008
Appetite	-5.8 ± 33 (47)	-10 ± 26 (25)	0.41	NS	NS	0.006
Tired	24 ± 32 (68)	13 ± 32 (41)	2.63	NS	NS	0.023
Fear	6.6 ± 18 (56)	5.6 ± 14 (38)	0.08	NS	NS	0.001
Happy	26 ± 20 (59)	30 ± 17 (44)	1.33	NS	NS	0.012
Want to be hugged	13 ± 19 (40)	13 ± 18 (34)	0.01	NS	NS	0.000
Want to hug	14 ± 19 (40)	13 ± 17 (34)	0.02	NS	NS	0.000
Vital signs parameters ΔE_{max}						
Systolic blood pressure, mmHg	25 ± 12 (87)	22 ± 13 (59)	1.24	NS	NS	0.008
Diastolic blood pressure, mmHg	14 ± 9 (87)	13 ± 10 (59)	0.11	NS	NS	0.001
Mean arterial pressure, mmHg	17 ± 9 (87)	17 ± 10 (59)	0.11	NS	NS	0.001
Heat rate beat/min	18 ± 15 (87)	17 ± 14 (59)	0.03	NS	NS	0.000
Rate pressure product, mmHg/min	4,561 ± 2,967 (87)	4,393 ± 2,746 (59)	0.06	NS	NS	0.000
Body temperature, °C	0.3 ± 0.5 (87)	0.2 ± 0.5 (59)	0.19	NS	NS	0.001
Adjective Mood Rating Scale rating ΔE_{max}						
Activity	2.3 ± 5.2 (87)	2.7 ± 4.9 (59)	0.26	NS	NS	0.002
High mood	2.8 ± 3.3 (87)	3.0 ± 3.0 (59)	0.18	NS	NS	0.001
Fear/depression	1.1 ± 3.7 (87)	0.9 ± 3 (59)	0.10	NS	NS	0.001

N, number of subjects; SD, standard deviation; NS, not significant; Δ, values are change scores from placebo; [a]p value additionally corrected for multiple comparisons according to the Nyholt method; η^2, eta square.

Nevertheless, this missing link between DA genetic variations and MDMA-related phenotypes might not solely be caused by a lack of genetic influence on the MDMA effects but rather the potentially minor role of DA in MDMA effects. Although MDMA is an amphetamine, it acts mainly on the 5-HT system and therefore leads to its classification as an entactogen (7, 62).

The present study has limitations. Although this analysis was done using the largest sample of healthy human subjects who received MDMA in placebo-controlled studies, the sample size is still relatively small when considering the partially small rare allele groups and mostly weak effect sizes for the influence of genetic variants on the MDMA response. This is especially influencing spurious, uncorrected effects (i.e., the AA carrier group for the SNP DRD2/ANKK1 rs1800497 with N = 2). Larger cohorts might show a more balanced sample distribution, which might lead to different results. Additionally, the study was conducted in healthy volunteers with a single dose of 125 mg MDMA. Therefore, the findings may not be applied to other populations and situations, such as psychiatric patients and the use of higher doses of MDMA. Furthermore, SNPs in genes of other targets of MDMA may also be involved. However, we corrected for the modulatory effects of known genetic variants that influence the metabolism of MDMA (17, 18) by taking interindividual differences in plasma MDMA concentrations into account. We also might have missed some relevant genetic polymorphisms. A novel potentially functional SNP within the DAT1 has been described in recent research. However, the SNP showed no significant alteration in the inhibition of DA uptake by MDMA in human embryonic kidney 293 cells (63). We have also not tested for rare haplotypes because a haplotype approach may lead to very small groups and more potential statistical artifacts. However, a haplotype suggested by Brewer et al., which consists of rs28363170 10/10 genotype and at least one rs3836790 5R-allele carriers, showed a reduced subjective response to cocaine compared to others (40). The same haplotype showed no effect in the present study. In fact, uncorrected results even implied opposite and incoherent effects, with 10R carriers showing lower MDMA-induced MAP changes and 5/5 carriers showing higher MAP changes than subjects with the 9/9 genotype or a 6R-allele, respectively. This incoherency may be attributable to the different substances used (cocaine vs. MDMA) and different cohorts (80% males of African descent vs. the sex-balanced sample of European descent) (40). Additionally, MDMA may interact with a different binding site on the DAT compared to other stimulants like cocaine (64). Finally, previous drug experiences were not equally distributed among DAT1 rs11133767 genotype groups, and effects might slightly depend on previous substance use experiences. Because of the involvement of DA in addiction, subjects carrying a TT genotype may be more prone to illicit substance use (65). Apart from this finding, given that our cohort included mostly

drug-naive subjects with limited drug use experience, some alleles associated with increased drug use might even be underrepresented. However, the tested variants were consistent with the Hardy–Weinberg equilibrium and comparable with frequencies found in European genome databases.

We conclude that the present findings align with previous studies in that variations in genes coding for players of the monoaminergic systems are unlikely to explain interindividual variations in the acute effects of MDMA in humans.

DATA AVAILABILITY STATEMENT

The datasets for this manuscript are not publicly available because the individual genotyping consent did not include storing in public repository. Requests to access the datasets should be directed to Matthias Liechti, Matthias.liechti@usb.ch.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission Nordwest- und Zentralschweiz (EKNZ). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PV analyzed the data and wrote the manuscript. ML conceived the study, obtained funding, and wrote the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00755/full#supplementary-material

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REVIEW
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Modulation of Social Cognition *via* Hallucinogens and "Entactogens"

Katrin H. Preller and Franz X. Vollenweider*

Neuropsychopharmacology and Brain Imaging, Department of Psychiatry, Psychotherapy, and Psychosomatics, University Hospital for Psychiatry Zurich, Zurich, Switzerland

Social cognition is a fundamental ability in human everyday lives. Deficits in social functioning also represent a core aspect of many psychiatric disorders. Yet, despite its significance, deficits in social cognition skills are insufficiently targeted by current treatments. Hallucinogens and entactogens have been shown to have the potential to modulate social processing. This article reviews the literature on the influence of hallucinogens and entactogens on social processing in controlled experimental studies in humans and elucidates the underlying neurobiological and neuropharmacological mechanisms. Furthermore, it identifies current knowledge gaps and derives implications for hallucinogen-assisted treatment approaches as well as the development of novel medication for trans-diagnostic impairments in social cognition.

Keywords: social cognition, psychedelics, serotonin, pharmacology, functional magnetic resonance imaging, emotions

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****Correspondence:***
Katrin H. Preller
preller@bli.uzh.ch

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INTRODUCTION

Humans are a social species (1). Social processes range from societal matters like politics, to more private every-day activities like being successful in a working environment, finding an apartment, romantic partnerships, and the use of virtual social networks. To be able to function in this social environment, we use capabilities which are subsumed under the term "social cognition" (2). Social cognition has been defined as mental processes through which we perceive, think about, and act toward other people (3). Critically, deficits in social functioning represent a core aspect and important diagnostic criterion of many—if not all—psychiatric disorders (4). Not only do difficulties in social interaction abilities increase the risk of developing a psychiatric disorder, but they also contribute to the maintenance or worsening of symptoms, as therapeutic processes as well as support seeking and re-integration into everyday activities, e.g., work-life, are social activities (4, 5). The importance of social cognition has also been recognized by the Research Domain Criteria (RDoC) initiative, which defines social processes as one of five trans-diagnostic dimensional constructs critical to human behavior and mental disorders (6–8). Yet, deficits in social cognition skills are insufficiently—if at all—targeted by current treatment approaches (9).

Hallucinogens are psychoactive substance which induce transient perceptual anomalies and an altered state of consciousness. The effect of entactogens is characterized by experiences of oneness and emotional openness. Entactogens as well as hallucinogens have been shown to successfully modulate social processing in rigorous scientific studies (10–12). This is important for two reasons (13): 1) In the search for novel medication for transdiagnostic social dysfunction in psychiatric disorders, these substances provide a powerful tool to increase our understanding of the neural mechanisms underlying social processing and behavior. Due to their well-investigated receptor pharmacology, in particular with regard to hallucinogens, they can identify novel targets for the

development of new therapeutics. 2) Given that drug development in psychiatry has stagnated for decades, new therapeutic models are urgently needed (14). Entactogens and hallucinogens have shown promising results in preliminary clinical trials in disorders also characterized by social impairments such as depression, anxiety, post-traumatic stress disorder (PTSD), and autism spectrum disorders (ASD) (15–19). These substances could, therefore, represent important adjuncts to psychotherapy in psychiatric disorders.

The first part of this review focuses on the effects of hallucinogens and entactogens on social cognition in clinical populations (*Modulation of Social Cognition in Clinical Populations*). *Acute Effects of Entactogens and Hallucinogens on Social Cognition in Healthy Volunteers* reviews the acute effects of entactogens and hallucinogens on social cognition in healthy volunteers. *Long-Lasting Effects in Healthy Participants* provides a summary of long-lasting hallucinogen- and entactogen-induced effects on social cognition, and *Neuropharmacological Underpinnings of Alterations in Social Cognition Induced by Hallucinogens and Entactogens* explores the neuropharmacological basis of these modulatory effects. This chapter is particularly important for informing the development of novel therapeutics targeting socio-cognitive deficits in psychiatric disorders. Complimentary to the work reviewed here, there is a broad body of literature on the effects of these substances on social cognition in animals (20). However, these studies are beyond the scope of this review and so will not be discussed here. Furthermore, this review focuses on experimental and controlled studies in humans and will not include literature on survey data or studies completed with recreational drug users. This review mainly discusses effects induced by two entactogens, 3,4-methylenedioxymethamphetamine (MDMA) and gamma-hydroxybutyrate (GHB), and two hallucinogens, lysergic acid diethylamide (LSD) and psilocybin. GHB, sometimes also referred to as liquid ecstasy, has been associated with the group of entactogens (21). However, it is important to note that the neuropharmacological mechanisms underlying GHB's psychotropic effects differ strongly from MDMA and serotonergic hallucinogens (22). Yet, given that GHB has been reported to be used recreationally for its prosocial effects, empirical studies on GHB are included in this review. Experimental research on the influence of other hallucinogens and entactogens on social functioning in humans is currently lacking and should be investigated in future studies.

MODULATION OF SOCIAL COGNITION IN CLINICAL POPULATIONS

Alterations in social processing may be important modulators of the clinical efficacy of entactogens and hallucinogens. MDMA-assisted psychotherapy has been shown to reduce social anxiety in autistic adults for up to 6 months after treatment (18). Twelve out of 19 PTSD patients interviewed 1 year after they had completed MDMA-assisted therapy reported enhanced relationships and social functioning as a benefit from participating in the treatment (23). The patients described increased empathy, communication with other people, and improved relationships with friends and family (23). These pro-social effects may be particularly important for preventing relapse and increasing the long-term success of MDMA-assisted therapy, since they may reduce social withdrawal and promote support seeking.

Recent preliminary studies on the efficacy of psilocybin in mood disorders and addiction have also shown promising results (16, 17, 24, 25). In an open-label pilot study, 12 out of 15 treatment-seeking smokers were nicotine abstinent 6 months after two to three administrations of psilocybin (26). In a follow-up interview participants identified social factors, i.e., smoking as a way of connecting with other people, that contributed to their addiction and reported psilocybin-induced feelings of love and connection with their environment and other people as important for quitting smoking (27). Furthermore, some patients described engaging more in prosocial and altruistic activities after their psilocybin sessions (27), raising the possibility that psilocybin may have re-instated social reward processing helping patients to overcome their addiction.

Furthermore, psilocybin has been shown to have beneficial effects in an open-label feasibility study in patients suffering from treatment-resistant depression (16). Three months after treatment, patients showed increases in extraversion and openness scores (28). Furthermore, Lyons & Carhart-Harris (29) reported a slight, but non-significant decrease in authoritarian political views in seven depressed patients 7–12 months after treatment with psilocybin. In this study, objective tests of emotion recognition and processing were conducted. On the FERT, the speed of emotional face recognition was increased 1 week after psilocybin treatment, an effect that correlated with reduced anhedonia (30). In contrast to results obtained during the acute effects of psilocybin in healthy participants (see *Empathy, Mentalizing, and Emotion Recognition*), amygdala reactivity was increased in response to fearful faces in treatment-resistant depressed patients the morning after psilocybin administration (31). It is therefore possible that psilocybin facilitates the processing of negative experiences acutely *via* a reduction of amygdala reactivity, rendering them more accessible and bearable. This may lead to increased reactivity and emotional processing post-acutely. However, increased amygdala reactivity toward fearful faces was measured prior to any psychological integration work (31). Therefore, long-term effects of psilocybin on amygdala reactivity and its clinical relevance still need to be determined in future studies. Yet, the same patients reported that they experienced a sense of disconnection from others as particularly distressing before psilocybin-assisted treatment (32). After treatment, many reported to be able to "re-connect" with family members, friends, strangers, and even people who had wronged them. Patients identified this increased connection as one of two main change processes in relation to treatment (32), supporting the idea that the influence of hallucinogens on social cognition and behavior may be an important mechanism underlying their clinical efficacy.

ACUTE EFFECTS OF ENTACTOGENS AND HALLUCINOGENS ON SOCIAL COGNITION IN HEALTHY VOLUNTEERS

Acutely, MDMA has been described as a prototypical entactogen and is recreationally used for its prosocial effects (20). It is also the substance most widely studied in relation to social perception. More recently, there has been growing interest the effects of hallucinogens, in particular LSD and psilocybin, on social cognition. Studies showed that, like MDMA, both psilocybin and LSD, significantly modulate social processing and have acute pro-social effects (11, 12, 33, 34). Recreationally, low doses of GHB have been reported to be used to increase sexual arousal (35).

Self-reported pro-social effects measured in scientific studies include increased trust and closeness to others. For example, after the administration of 1.5 mg/kg MDMA participants reported a significantly increased desire to engage in social activities (36), as well as increased pleasantness of affective social touch (37). When given the opportunity, MDMA participants also spent more time interacting with others, particularly after a low dose (0.5 mg/kg) (38). Furthermore, MDMA (125 mg) increased the subjective experience of being close to others and trusting others by approximately 25% during peak effects (10, 39). Increases in closeness and trust during peak effects after LSD administration (200 µg) have been shown to be in a similar range (33, 40). GHB (20 mg/kg) has been reported to increase the tendency to talk (41).

The following chapters provide a detailed overview of the acute effects of MDMA, GHB, psilocybin, and LSD on different objective measures of social cognition, including empathy, mentalizing, and emotion recognition, moral and altruistic behavior, social rejection sensitivity, social influence, sexual arousal and perception of romantic relationships, and social influence processing. A summary of the results is provided in **Figure 1**.

Empathy, Mentalizing, and Emotion Recognition

Empathy has been defined as the ability to vicariously experience and/or understand the affect of others, and is thought to be critical for prosocial behavior (42). Empathy is impaired in a number of psychiatric disorders, including depression, addiction, borderline personality disorder, and psychopathy (43–46). However, empathy is a multidimensional construct, comprising of both emotional and cognitive components (43). The emotional aspect of empathy describes a person's emotional reaction to another's emotional state, i.e., the ability to feel what another person feels (47). Cognitive empathy refers to the ability to take another person's perspective and the understanding of another person's mental state, without necessarily being in the same affective state (47). Thus, cognitive empathy strongly overlaps

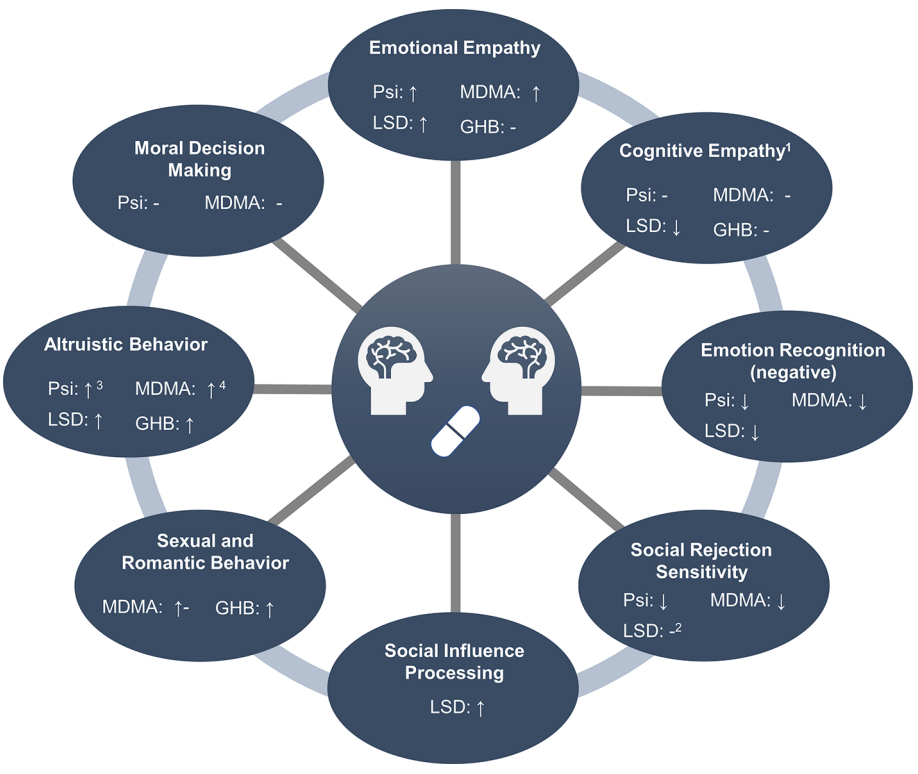

FIGURE 1 | Overview of social processes modulated by entactogens and hallucinogens. [1]Measured with the Multifaceted Empathy Test. [2]Only assessed after the administration of low doses (≤26 µg). [3]Assessed in male participants only. [4]In men and when directed toward friends, but not strangers.

with the concepts of affective theory of mind, mentalizing, and emotion recognition (48).

Various tasks have been applied to study empathy after the administration of hallucinogens and entactogens. The Multifaceted Empathy Task [MET (49)] captures both, emotional and cognitive empathy. Participants are asked to rate emotional pictures on induced emotional concern and arousal (emotional empathy). Furthermore, participants are asked to identify the mental state the person depicted is in (cognitive empathy). Additionally, cognitive empathy has been assessed using tasks such as the Movie for the Assessment of Social Cognition (MASC), the Reading the Mind in the Eyes Task (RMET), as well as different versions of the Facial Emotion Recognition Task (FERT). The MASC is a video-based test of mentalizing and therefore represents the most ecologically valid test of cognitive empathy (50). The REMT, like the MET, requires participants to infer the mental state of a person in a photograph by choosing which of four words provided along with the picture describes best what the person in the picture is feeling. However, while the MET displays everyday life situations conveying information on emotional mental states *via* facial expression, body language, and context, the RMET focuses exclusively on the eye region. The FERT constitutes a further emotion recognition task. In most versions, different intensities of facial emotions are presented making it possible to calculate the intensity that is necessary for an emotion to be detected correctly, but unlike the MASC and MET does not depict whole sceneries.

Various studies have consistently shown that MDMA modulates emotional empathy, assessed using the MET (49). An overview of all results is presented in **Table 1**. One hundred twenty-five milligrams as well as 75 mg MDMA increased emotional empathy (10, 51, 52). In two studies this increase was particularly pronounced in response to positive stimuli and in male participants (10, 51). A third study did not find an influence of valence (52). A pooled analyses of these data confirmed the MDMA-induced increase in emotional empathy in particular for positive emotions, but did not find an influence of sex or trait empathy (62). However, one study, showed contrary results reporting no influence of 100 mg of MDMA on emotional empathy in male participants (53).

Like MDMA, LSD has been shown to increase emotional empathy, assessed with the MET. LSD dose-dependently increased emotional empathy with significant effects at 200 µg (33). In line with results obtained under the influence of MDMA, enhanced emotional empathy under LSD was not modulated by trait empathy (12). However, while the LSD-induced increase in emotional empathy was particularly pronounced for positive stimuli, the psilocybin-induced (0.215 mg/kg) increase in emotional empathy was shown to be independent of valence (12). In contrast to MDMA and LSD, GHB (20 mg/kg) was not shown to affect emotional empathy (41).

While the increase in emotional empathy after the administration of MDMA, psilocybin, and LSD is mostly consistent across studies and substances, their effect on cognitive

TABLE 1 | Effects of entactogens and hallucinogens on empathy, mentalizing, and emotion recognition.

Drug	Doses	Emotional empathy	Cognitive empathy			Emotion recognition		References
		MET	MET	MASC	RMET	FERT/ Affective Bias Task	Emotional face reactivity	
MDMA	75 mg	↑[1]	–	–	–	–		51, 52
MDMA	100 mg	–	–			↓[2]		53
MDMA	125 mg	↑[1]	–		↑↓[3]	↓[2]		10, 39, 54
MDMA	0.75 mg/kg				–	–	–	36, 37, 55, 56
MDMA	1.5 mg/kg				–	↓[2]	↑[4]	36, 37, 55, 56
GHB	20 mg/kg	–	–	--				41
Psilocybin	0.115 mg/kg						↓[5]	57
Psilocybin	0.160 mg/kg						↓[6]	58
Psilocybin	0.170 mg/kg						↓[7]	59
Psilocybin	0.215 mg/kg	↑	–		↓[2]			12, 60
LSD	100 µg	–	↓			↓[2]	↓[8]	33, 61
LSD	200 µg	↑[9]	↓			↓[2]		33

[1]*Predominantly in male participants and for positive stimuli.*

[2]*For negative emotions.*

[3]*Decreases for negative emotions, increases for positive emotions.*

[4]*Increased zygomatic ("smile") muscle activity in response to happy facial expressions, increased visual attention to happy faces.*

[5]*Reduced response to negative emotions (EEG).*

[6]*Connectivity changes during negative and positive facial emotion processing (fMRI).*

[7]*Reduced neural response to negative and positive facial emotions (EEG).*

[8]*Reduced neural response to negative emotions (fMRI).*

[9]*For positive stimuliMET, Multifaceted Empathy Test; MASC, Movie for the Assessment of Social Cognition; FERT, Facial Emotion Recognition Task; empty cells indicate that this measure was not collected.*

empathy is less clear. Performance on the MASC has been studied after the administration of GHB (20 mg/kg), but did not reveal significant results (41). Similarly, MDMA (75 mg) administration did not induce significant modulations on the MASC (61). In line with this, MDMA (75, 100, & 125 mg), GHB (20 mg/kg), and psilocybin (0.215 mg/kg) did not affect cognitive empathy on the MET (10, 12, 51–53, 62). In contrast, LSD (100 and 200 µg) decreased cognitive empathy on the MET (33). In line with results obtained with the MET, two studies did not find an effect of MDMA (0.75 mg/kg, 1.5 mg/kg, and 75 mg) on the RMET (52, 55). However, a third study reported that MDMA (125 mg) increased the recognition of positive and decreased the identification of negative emotions (54). Psilocybin (0.215 mg/kg) decreased the recognition of negative emotions on the RMET (60).

Testing the performance on the FERT, Schmid et al. (57) did not find any effects after the administration of 75 mg MDMA. However, a 100 mg dose of MDMA decreased the accuracy of identifying fear and anger on a similar task (53). Additionally, a 125 mg dose of MDMA impaired the identification of fearful faces (39) and of fearful, angry, and sad faces, particularly in women, in a second study (10). This is in line with further results showing that 1.5 mg/kg but not 0.75 mg/kg MDMA decreased the accuracy of fear recognition (55) and anger and fear recognition (36). Furthermore, Wardle and de Wit (56) reported that MDMA (1.5 mg/kg) increased the intensity required to identify anger. No effects were found for a lower dose (0.75 mg/kg) or other emotions including fearful facial expressions. In the same study, MDMA (1.5 mg/kg) reduced corrugator ("frown") muscle activity to happy facial expressions in female participants and increased zygomatic ("smile") muscle activity to happy facial expressions in all participants. No effects were found while viewing negative emotions (56). When presented with pairs of faces (one neutral face and one emotional expression face) 1.5 mg/kg, but not 0.75 mg/kg MDMA, increased visual attention to happy faces, but not to negative emotions (37).

Emotion recognition has also been investigated after the administration of hallucinogens. Emotional face identification was not altered by small doses ("microdoses," 6.5, 13, and 26 µg) of LSD (63). However, psychedelic doses of LSD (100 and 200 µg) impaired the recognition of fearful and sad faces on the FERT (33). In line with this, the administration of LSD (100 µg) reduced the neural response to fearful vs. neutral faces in the left amygdala and the right medial frontal cortex (61). Psilocybin (0.115 mg/kg) also reduced the subjective discrimination between fearful and neutral faces and the encoding of fearful faces measured with EEG expressed by reduced N170 responses (57). The processing of happy faces was not affected (57). However, after the administration of 0.170 mg/kg two time periods of psilocybin-induced modulation of emotional face processing were identified: during the 168–189 ms interval decreased activity in response to both neutral and fearful faces within limbic areas, including amygdala and parahippocampal gyrus, and the right temporal cortex was observed, and over the 211–242 ms interval reduced activity in response to happy faces within limbic and right temporo-occipital brain areas was observed (59). Investigating the effect of psilocybin (0.160 mg/kg) during the discrimination of angry, happy, and fearful *vs.* neutral faces on amygdala seed-to-voxel connectivity *via* functional magnetic resonance imaging (fMRI) showed that psilocybin decreased the connectivity between the amygdala and the striatum during angry face discrimination. The connectivity between the amygdala and the frontal pole was decreased during happy face discrimination. No effect was observed during discrimination of fearful faces (58).

In sum, both hallucinogens and the entactogen MDMA, but not GHB, have been shown to acutely increase emotional empathy in controlled experimental trials. This effect seems to be more pronounced for positive emotions, in particular after the administration of MDMA. Cognitive empathy and mentalizing, i.e., the ability to correctly infer another person's mental state, was mostly unchanged by hallucinogens and entactogens. Reduced emotional but preserved cognitive empathy has been reported in patients suffering from substance use disorders (46). Facilitating the reconnection with their social environment *via* increased emotional empathy may therefore contribute to clinical efficacy of hallucinogens shown in preliminary studies with addicted patients (24, 26). In contrast to psilocybin and MDMA, LSD decreased the correct interpretation of ecologically valid stimuli (33) and psilocybin decreased the ability to infer negative emotions from the eye region (60). In one study, MDMA decreased the decoding of negative emotions from the eye region, while at the same time increasing this ability for positive stimuli (54). These results are in line with reduced recognition and processing of predominantly negative emotional faces after the administration of higher doses of MDMA and at all doses tested (low-high) of psilocybin and LSD. The increased empathy for positive emotions and decreased recognition of negative emotions shown in these studies is in line with the interpretation by Bedi et al. (55) that a decreased ability to identify negative emotions might facilitate social approach behavior and thus social interaction. This effect might be clinically relevant, since it may reduce social withdrawal behavior and improve the patient-therapist relationship during hallucinogen-assisted treatment. However, this hypothesis remains to be tested by future studies.

Moral and Altruistic Behavior

Moral and altruistic behaviors are fundamental for a functioning society (64). Despite its significance, to date the neuropharmacology of moral behavior has been scarcely investigated. Using moral dilemma tasks, it has been shown that neither MDMA (75 mg) nor psilocybin (0.215 mg/kg) influenced moral decision making (12, 51). However, no other studies have investigated the influence of hallucinogens or entactogens on moral behavior.

To understand the effects of hallucinogens and entactogens on altruistic behavior, most studies implemented resource allocation tasks. On the Social Value Orientation Test (SVO) participants act altruistically when choosing an option that maximizes the allocation for another person. While MDMA did not change behavior on the SVO when administered in a lower dose (75 mg) (51), male participants made more altruistic choices after the administration of 125 mg MDMA (10). No effect was found for female participants, potentially because they already showed

high altruistic behavior following placebo administration (10). Another study employed a similar paradigm, the Welfare Trade-Off Task, and reported that participants showed more altruistic behavior after the administration of 1 mg/kg MDMA, but only if the other person was a friend, not a stranger (65). This is in line with another study showing that MDMA (75 mg) did not influence trust or reciprocity during a Trust Game played with an unknown partner (52). However, the effects of MDMA on trust and reciprocity toward a close friend were not assessed in this study. Modulation of altruistic behavior after MDMA administration therefore seems to depend on dose, gender, and social proximity. Increased altruistic behavior on the SVO was also induced by LSD (100 and 200 µg, combined groups) (33). After GHB (20 mg/kg) administration, participants also showed more altruistic behavior on the SVO and a Charity Donation Task, but only after participants who scored high at baseline were excluded from the analysis (41). No effect was found for reciprocity during a Trust Game after GHB administration (41).

Investigating allocation behavior in more reciprocal tasks, Gabay et al. (66) showed that psilocybin (2 mg, i.v.) as well as MDMA (100 mg) reduced altruistic punishment, i.e., punishment of social norm violations which are costly to the self, in the Ultimatum Game in male participants. Furthermore, Gabay et al. (53) found that male participants behave more cooperatively when interacting with trustworthy partners and show greater recovery from breaches of trust during an iterated prisoner's dilemma after the administration of MDMA (100 mg). However, results on economic allocation games are often difficult to interpret, especially in studies investigating the effects of substances that induce altered states of consciousness. While data on reward sensitivity were collected in the MDMA condition, this was not the case for the psilocybin condition (66). It is conceivable that psilocybin may alter sensitivity to financial rewards, rendering the interpretation of allocation tasks involving monetary rewards more challenging.

In sum, hallucinogens and entactogens have been shown to increase altruistic behavior. However, it is important to bear in mind the following caveats: these substances may also alter sensitivity to financial rewards; increases in altruistic behavior may occur only in participants with low altruism at baseline; and finally increases in altruistic behavior may occur only when directed toward a friend. A summary is presented in **Table 2**. Even though the effects of hallucinogens and entactogens on prosocial behavior seem to be complex and dependent on factors such as social proximity and baseline altruism, they may be important within a therapeutic framework as increases in altruism may support reconnection with the patients' social environment. In contrast to altruistic behavior, no effect has been found on moral decision making as measured with moral dilemma tasks. It is conceivable that hallucinogens and entactogens do not impact moral behavior, yet it is also possible that higher doses are needed to change moral decision making. Additionally, it is noteworthy that moral dilemmas often include violent and negative actions and outcomes. Yet, it has been shown that hallucinogens reduce the processing of negative stimuli. It is therefore possible that moral dilemmas were less salient after psilocybin administration. Lastly, post-acute effects of hallucinogens and entactogens have not been examined yet. It may be possible that changes in moral behavior only occur post-acutely.

Social Rejection Sensitivity

Increased sensitivity to social rejection and exclusion is observed in many psychiatric disorders (67–69). At the same time, psychiatric patients frequently encounter social rejection (70). Normalizing increased rejection sensitivity could therefore be clinically relevant to avoid being trapped in a vicious circle that ultimately leads to social withdrawal, reduced support, and the worsening of clinical symptoms.

A commonly used paradigm to investigate the reaction to social rejection is called "Cyberball." This paradigm consists of

TABLE 2 | Effects of entactogens and hallucinogens on moral and altruistic behavior.

Drug	Doses	Moral behavior	Altruistic behavior				Reciprocity/trust		References
		Moral Dilemmas Task	Social Value Orientation Test	Welfare Trade-Off Task	Charity Donation Task	Ultimatum game	Trust game	Prisoner's dilemma	
MDMA	75 mg	–	–				–		51, 52
MDMA	1 mg/kg			↑[1]					65
MDMA	100 mg					↑[2]		↑[2]	53, 66
MDMA	125 mg		↑[2]						10
GHB	20 mg/kg		↑[3]		↑[3]		–		41
Psilocybin	0.215 mg/kg	–							12
Psilocybin	2 mg, i.v.					↑[2]			66
LSD	100 and 200 µg								33

[1]*Only toward friends, not strangers.*
[2]*Only in male participants.*
[3]*Only after participants were excluded who scored high at baseline*
empty cells indicate that this measure was not collected.

an interactive virtual ball-tossing game that simulates a real-life interactive experience of social exclusion (71). While in the beginning participants are usually equally involved in the game, one player is eventually excluded. In most studies, the participants themselves are the ones who are excluded and therefore rejected by the other players, which reliably induces feelings of "social pain" (72).

MDMA (0.75 and 1.5 mg/kg) has been shown to reduce the effect of social rejection on self-reported lower mood and self-esteem. The higher dose of MDMA (1.5 mg/kg) additionally increased the perceived percentage of throws received in the rejection condition (73). However, no modulatory effects of MDMA (75 mg/kg) on the reaction to social exclusion were found when only one of three players was excluding the participant (52). Social exclusion often leads to social stress (74). Yet, MDMA (0.5 and 1.0 mg/kg) did not alter the response to social stress in the Trier Social Stress Test (75).

The effect of LSD on social rejection induced by the Cyberball game has so far only been tested with very low doses ("microdoses"). Bershad et la. (63) (in press) reported that 6.5, 13, and 26 μg did not modulate the perceived number of received ball throws or influenced mood responses to rejection. Preller et al. (11) combined the Cyberball paradigm with fMRI and MRS measurements to study the effects of psilocybin on social rejection processing. After psilocybin (0.215 mg/kg) administration, participants reported a reduced feeling of social exclusion, while at the same time no significant differences were found between placebo and psilocybin with regard to perceived number of received ball throws. Furthermore, the neural response to social exclusion was decreased in the dorsal anterior cingulate cortex and the middle frontal gyrus, key regions for social pain processing. This reduction in the "social pain signal" was significantly correlated with decreased aspartate content. Furthermore, it correlated with psilocybin-induced alterations in self-processing, i.e., experience of unity (11). This is in line with a study showing that hallucinogen-induced alterations in self-processing and social cognition are intertwined (34). Such findings may be of particular interest in the treatment of psychiatric disorders characterized by an increased self-focus like depression (76). Hallucinogen-induced alterations in self-processing such as the experience of unity may reduce self-focus and concurrently improve social functioning.

In sum, psilocybin has been shown to attenuate the processing of negative stimuli which extends to negative social interaction (11, 77). While participants under the influence of psilocybin were able to correctly guess the number of received ball throws indicating that they were fully aware of being excluded, their self-reported emotional response was decreased in line with a reduction in the "social pain signal" in the anterior cingulate cortex (11). However, MDMA reduced self-reported negative effects of social exclusion, but also increased perceived ball throws, potentially indicating reduced awareness of social exclusion (73). It is therefore possible that both substances reduce the processing of social rejection *via* different mechanisms. It is also conceivable that reducing rejection sensitivity is critically involved in the potential therapeutic effects of entactogens and hallucinogens, in particular with respect to therapist–patient interaction. However, this hypothesis has not yet been tested in clinical populations. Finally, the effects of entactogens and hallucinogens on social rejection processing other than psilocybin and MDMA still need to be investigated in future studies.

Sexual Arousal and Perception of Romantic Relationships

Engaging in romantic relationships and sexual behavior is an intimate social process and disturbances of close inter-personal relationships are prominent in psychiatric disorders (78). Yet, only a few neuropsychopharmacological studies have so far explored this aspect of social cognition. To date, no studies have experimentally investigated how hallucinogens influence sexual arousal or the perception of romantic relationships. Studies on the effects of entactogens on these processes are more common. After the administration of MDMA (125 mg), participants reported increased sexual arousal and desire (39). Furthermore, participants used more sexual and social words when discussing a close personal relationship after the administration of 1.5 mg/kg MDMA (79). On the Sexual Arousal Task, a computerized task presenting neutral as well as implicit and explicit sexual pictures, participants treated with MDMA (75 mg) sought to increase the presentation time of implicit sexual stimuli, however they did not report alterations in sexual arousal while viewing the images (80). Furthermore, no effect was found on the evaluation of romantic relationships of others (80) or on attractiveness ratings (36). Together, these results suggest only subtle, subjective effects of MDMA on sexual arousal and perception of intimate relationships, but may reflect an increased willingness to disclose personal information (79).

GHB has been reported to have pronounced effects on self-reported sexual arousal (81). In an experimental setting, GHB (20 and 35 mg/kg) dose-independently increased self-reported sexual arousal and desire (82). Furthermore, participants reported more sexual arousal while viewing erotic as well as neutral stimuli (82). Together, these results point to a prosexual effect specific for GHB. However, more research is needed to also determine the effects of hallucinogens on sexual arousal and the perception of intimate relationships.

Social Influence Processing

Very little research has been conducted to investigate the effect of hallucinogens and entactogens on suggestibility and social influence processing, despite the fact that it is highly relevant for therapeutic interaction. So far, only two studies have been conducted, both investigating the influence of LSD on suggestibility (83, 84). The first study, which was limited by a small sample of 10 healthy volunteers, showed that LSD (40–80 μg, i.v.) enhances suggestibility on the Creative Imagination Scale, while Cued Imagery remained unaffected (83). A second study showed that LSD (100 μg, p.o) increases adaptation to opinions expressed by a norm group, but only if those opinions were not too different from the participants own (84). Furthermore, this study showed that increases in blood oxygen level-dependent signal in medial prefrontal regions were associated with altered social feedback processing. It is therefore conceivable that hallucinogens influence

how participants process social feedback and how they integrate this feedback to subsequently make decisions. This finding has direct clinical relevance for therapists working with these substances within the framework of hallucinogen-assisted therapy. Furthermore, the impact of alterations in social feedback processing in a clinical setting should be evaluated and therapists trained accordingly.

LONG-LASTING EFFECTS IN HEALTHY PARTICIPANTS

While it has repeatedly been shown that hallucinogens increase the personality trait openness (85, 86), experimental studies investigating the long-term effects of entactogens and hallucinogens on social cognition and behavior remain scarce.

It has been reported that recreational MDMA users showed increased cognitive, but not emotional, empathy compared to controls on the MET and the MASC (87, 88). Furthermore, they exhibited less-self-serving behavior on a money allocation task played with a stranger (87). Interestingly, these social functions were not influenced by acute administration of MDMA in controlled studies (10, 51, 52). However, cross-sectional investigations in recreational drug users have to be interpreted with caution as they do not allow for causal inference. It is therefore possible that MDMA has post-acute positive effects on cognitive empathy and altruistic behavior, but it is also conceivable that people with high cognitive empathy and prosocial motivation are more prone to recreationally use MDMA. To test these hypotheses, the long-term effects of MDMA on social cognition in healthy individuals need to be investigated in future experimental and controlled studies.

Self-reported increases in interpersonal closeness and positive/altruistic social effects were reported 1, 2, 6, and 14 months after one and two administrations of psilocybin (89–92). Self-reported increases in positive/altruistic social effects were also shown 12 months after the administration of LSD in healthy participants (93). However, the personality trait openness was not influenced by LSD administration in this study (93).

Objective data on the long-term effects of hallucinogens on social processes is still scarce. Mason et al. (94) reported that emotional empathy on the MET was increased the morning after a psilocybin retreat. This increase was still significant after seven days, but only for negative emotions. Given the lack of further data on objective long-term effects, future studies are needed to evaluate whether hallucinogens and entactogens have a lasting impact on social processes.

NEUROPHARMACOLOGICAL UNDERPINNINGS OF ALTERATIONS IN SOCIAL COGNITION INDUCED BY HALLUCINOGENS AND ENTACTOGENS

Understanding the neuropharmacological underpinnings of alterations in social cognition induced by hallucinogens and entactogens is vital to accelerate the development of novel medication for transdiagnostic social dysfunction in psychiatric disorders. MDMA, GHB, psilocybin, and LSD engage with various targets in the brain. To assess the neuropharmacological mechanisms underlying the prosocial effects of these substances, studies have investigated the neuroendocrinology after drug administration, the effects of these substances after blocking specific receptors or transporters, and have compared the effects between substances with different mechanisms of action.

MDMA interacts with numerous transporters and receptors in the brain. It releases 5-HT, NE, and, to a lower extent, DA from nerve terminals *via* action on monoamine transporters, and increases plasma levels of oxytocin, prolactin, and cortisol (10). MDMA is also a low-potency partial agonist of 5-HT receptors (95–97). GHB has direct agonist effects on GHB- and $GABA_B$-receptors and neuromodulatory properties on glutamate, dopamine, serotonin, norepinephrine, and cholinergic transmission (22). Furthermore, GHB has been shown to increase plasma progesterone, but not oxytocin or testosterone levels (41).

Molecular studies have shown that the psychoactive metabolite of psilocybin, psilocin, binds to various serotonin receptors (PDSP database: https://pdsp.unc.edu/databases/kidb.php). Psilocin has high affinity and agonist activity on the 5-HT_{2A} receptor and this receptor subtype is critically implicated in psilocybin-induced effects (98). Additionally, recent evidence in humans also suggests the involvement of the 5-HT_{1A} receptor in mediating the effects of psilocybin (99). LSD has predominantly agonist activity at 5-HT2A/C, −1A/B, −6, and −7 and dopamine D2 and D1 receptors. Administering the 5-HT_{2A} receptor antagonist ketanserin before LSD administration has been shown to block LSD-induced effects, implicating activity on this receptor as vital for its effects (100).

To date, only few studies have investigated the pharmacology of MDMA-induced alterations in social cognition *via* blocking specific receptors. Kuypers et al. (52) showed that the mixed beta-adrenoreceptor blocker/5-HT_{1A} antagonist pindolol did not block MDMA-induced increases in emotional empathy. A further study showed that neither duloxetine, which inhibits MDMA-induced monoamine transporter-dependent serotonin and norepinephrine release, reboxetine, which inhibits MDMA-induced norepinephrine release, nor clonidine, which inhibits MDMA-induced transporter-independent vesicular release of norepinephrine, blocked the observed increases in decoding accuracy for positive and impaired decoding accuracy for negative stimuli on the RMET after MDMA administration (54). However, duloxetine was most effective in reducing the acute subjective MDMA effects, implicating the serotonin system as a key mechanism of action (54). This is in line with results reported by Kuypers et al. (101) showing that an MDMA-induced reduction of arousal in response to negative sounds was blocked by the 5-HT_{2A} receptor antagonist ketanserin.

The neuropeptide oxytocin has repeatedly, although not unanimously, been related to social behavior (102). Therefore, MDMA-induced increases in oxytocin levels are another candidate mechanism potentially underlying MDMA's prosocial effects. However, so far, no study investigating the relationship between MDMA-induced effects and oxytocin plasma levels has found significant correlations with regard to social processing

and behavior. For example, increases in emotional empathy, impaired identification of negative emotions, enhanced decoding of positive facial expressions, and increased altruistic choices after MDMA administration were not related to oxytocin plasma levels or other neuroendocrine effects (10, 51, 52, 54). In line with this, comparing the effects of MDMA directly with oxytocin showed differential effects of the two substances. Kuypers et al. (52) investigated the effects of MDMA and oxytocin in a within-subject design and reported that while MDMA increased emotional empathy, oxytocin did not affect measures of empathy or other social cognitive outcomes. A further study reported that, in contrast to MDMA, intranasal oxytocin enhanced recognition of negative emotional faces (36). Additionally, only modest correlations between the effects of MDMA and oxytocin in the same individuals were found. The effects of MDMA (1.5 mg/kg) on social cognition were also substantially more pronounced than the ones induced by oxytocin (40 IU) (36). Together, these results provide limited support for the hypothesis that increases in oxytocin levels underlie the prosocial effects of MDMA. This is in contrast to animal studies indicating that oxytocin plays an important role in MDMA-related social effects (103, 104). Being beyond the scope of the current review, future work should address these discrepancies between human and animal data.

Additionally, a number of studies have compared the effects of MDMA with other amphetamines as well as with modafinil. These studies indicated that MDMA has a different effect profile than other amphetamines. In contrast to MDMA, methylphenidate and modafinil increased misclassifications of emotions as angry on the FERT while MDMA increased misclassifications as happy (39). This is in line with another study showing that methylphenidate, but not MDMA, increased ratings of sexual arousal for explicit sexual stimuli (80). Neither MDMA nor methylphenidate altered appraisal of romantic relationships (80). Furthermore, methylphenidate lacked the empathy enhancing properties of MDMA (51). When compared with methamphetamine, Bershad et al. (37) showed that MDMA, but not methamphetamine, enhanced ratings of pleasantness of experienced affective touch and increased attention toward happy faces. These results indicate that the dopaminergic system, but not serotonergic neurotransmission may be involved in enhancing sexual drive, whereas the serotonin system may be involved in increasing empathy.

To illuminate the pharmacology of GHB-induced prosocial effects, one study investigated the relationship between GHB-induced alterations in outcomes on social tasks and neuroendocrine effects (41). No correlations were found between GHB-induced neuroendocrine effects and social behavior, but low progesterone levels at baseline were predictive of altruistic behavior on the SVO and a Charity Donation Task after GHB administration. This indicates that GHB induced prosocial behavior specifically in individuals with low progesterone levels (41).

Hallucinogens have been reported to exert their prosocial effects predominantly *via* agonism at the 5-HT_{2A} receptor and potentially in parallel with downstream effects on aspartate metabolism (11). Decreased recognition of negative emotions induced by psilocybin on the RMET was blocked by pretreatment with the 5-HT_{2A} receptor antagonist ketanserin (51). In line with this, LSD-induced effects on joint attention processing, self/other differentiation, and social influence processing were blocked by ketanserin (34, 84). Comparing the effects of psilocybin to those of the N-methyl-d-aspartate receptor antagonist ketamine, Schmidt et al. (57) reported differential effects, with psilocybin reducing the processing of negative faces, whereas ketamine induced an emotional blunting characterized by reduced encoding of both, negative and positive facial expressions.

Given these pharmacological results as well as the similarity of effects induced by MDMA and hallucinogens, it is conceivable that prosocial effects, in particular increased empathy and altruistic behavior, are modulated by a common mechanism, namely 5-HT_{2A} receptor stimulation. However, the functional and modulatory contribution of other receptors stimulated by these substances is scarcely investigated, in particular with regard to hallucinogens. Additional studies are needed that investigate the role of these receptor systems by selectively blocking them to comprehensively uncover the neuropharmacology underlying hallucinogen-induced modulations of social cognition. GHB which targets mainly GHB and $GABA_B$ receptors has a different effect profile implicating these receptors together with the dopamine system in prosexual effects. It has to be noted that entactogens and hallucinogens are not the only psychoactive substances that modulate social cognitive functioning. For example, alcohol has been reported to facilitate social interaction (105). While this is beyond the scope of the current review, the differential effects hallucinogens, entactogens, and other psychoactive substances should be discussed in future articles to systematically increase our understanding of the pharmacology of social cognition.

CONCLUSION

The current literature on experimental and controlled investigations of the influence of hallucinogens and entactogens shows that these substances are potent modulators of social cognition and behavior. While MDMA is recreationally used for its prosocial effects, this review shows that hallucinogens such as LSD and psilocybin similarly impact social cognitive measures. GHB, however, has been shown to have predominantly prosexual effects and may therefore not be classified as a typical entactogen. As described in detail in *Neuropharmacological Underpinnings of Alterations in Social Cognition Induced by Hallucinogens and Entactogens*, agonism on the 5-HT_{2A} receptor may be a common mechanism of classic hallucinogens and MDMA which underlies their prosocial effects. This is particularly important for the development of highly needed novel therapeutics targeting social deficits in psychiatric patients. Furthermore, these results implicate alterations in social processing as key mechanisms for the efficacy of psilocybin- and MDMA-assisted therapeutic approaches. In addiction disorders, the reinstatement of social reward processing may support reductions in drug intake and help overcome addiction. In anxiety and mood disorders, MDMA and hallucinogens may promote re-connection with patients' social environment as well as support seeking and reductions

in social withdrawal. Acutely, MDMA and hallucinogens may also enhance the patient-therapist relationship. Thus, it is vital that therapists working with MDMA and hallucinogens are aware of the acute effects of these substances on social cognition, including potential increases in suggestibility.

Despite recent efforts to elucidate the effects of hallucinogens and entactogens on social cognition, major knowledge gaps remain. Studies specifically investigating the dose-dependency of modulations in social cognition induced by hallucinogens and entactogens are still scarce, in particular regarding psilocybin. LSD and MDMA have shown some dose-dependent effects on empathy and altruistic behavior (10, 33, 51), indicating that robust modulations are measurable at doses of 100 mg MDMA/100μg LSD and above. Controlled studies on very low doses, so-called "microdoses," are still rare. Bershad et al. (63) did not find an effect of doses <30 μg LSD on social rejection sensitivity and emotional face identification. Further studies investigating dose-dependency in within-subject designs are needed. Furthermore, the impact of hallucinogens other than LSD and psilocybin on social cognition has not yet been investigated. Sex-specific effects are poorly understood. It has been shown that MDMA enhances emotional empathy predominantly in male participants (10). Furthermore, altruistic behavior after psilocybin administration was only investigated in males (66). Despite their potential clinical relevance, further systematic investigations into sex-specific drug effects are lacking. Data on effects after the acute phase of substance action are often missing. The neural mechanisms underlying changes in social cognition after administration of hallucinogens and entactogens are poorly understood. Differential effects of specific receptor systems targeted by these substances need to be investigated. Objective data on social behavior within the framework of MDMA- and hallucinogen-assisted therapy are still lacking. Studies on entactogens and hallucinogens have consistently shown prosocial effects and have identified alterations in social processing and behavior as key factors for the efficacy of treatments involving these substances. Thus, investigating these questions is a promising way to increase our mechanistic, neuropharmacological understanding of social processes, advance the development of novel therapeutics, and to uncover the full potential of these substances in clinical contexts.

AUTHOR CONTRIBUTIONS

KP has written the manuscript. FV has revised the manuscript.

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SYSTEMATIC REVIEW
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Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials

Juan José Fuentes[1], *Francina Fonseca*[1,2,3], *Matilde Elices*[1,4], *Magí Farré*[5,6] *and Marta Torrens*[1,2,3]*

[1] Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain, [2] Addiction Research Group (GRAd), Neuroscience Research Program, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain, [3] Psychiatry Department, Universitat Autònoma de Barcelona (UAB), Cerdanyola del Vallès, Spain, [4] Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain, [5] Clinical Pharmacology Department, Hospital Universitari Germans Trias i Pujol (IGTP), Badalona, Spain, [6] Pharmacology Department, Universitat Autònoma de Barcelona (UAB), Cerdanyola del Vallès, Spain

Lysergic acid diethylamide (LSD) was studied from the 1950s to the 1970s to evaluate behavioral and personality changes, as well as remission of psychiatric symptoms in various disorders. LSD was used in the treatment of anxiety, depression, psychosomatic diseases and addiction. However, most of the studies were not performed under contemporary standards, and it has taken several decades for a resurgence of interest in LSD research and its therapeutic potential for psychiatry. The aim of this review is to identify controlled and randomized clinical trials that assess the potential use of LSD in psychiatry. PRISMA guidelines for systematic review were followed. A literature search of PubMed and Psychedelic bibliography from Multidisciplinary Association for Psychedelic Studies (MAPS) databases was performed as well as a manual search of references from evaluated studies. Only randomized-controlled clinical trials were included. Study quality was systematically calculated by using the Cochrane Collaboration Tool for assessing risk of bias. A final selection of 11 articles was made after considering inclusion and exclusion criteria. LSD was administered to 567 patients in a dose ranging from 20 to 800 mcg. Despite the design heterogeneity of clinical trials, positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology, mainly in alcoholism. The vast majority of authors describe significant and positive short-term changes in patients, despite the fact that in some studies an important homogenization was observed between the LSD treatment group and control group at long-term follow-up. Multiple variables regarding LSD treatment therapeutic approach and quality of experience were revealed and related to therapeutic outcomes. LSD is revealed as a potential therapeutic agent in psychiatry; the evidence to date is strongest for the use of LSD in the treatment of alcoholism. Despite the difficulty of designing proper double blind clinical trials with this substance, new studies that conform to modern standards are necessary in order to strengthen our knowledge on its use and open new doors in the future.

Keywords: lysergic acid diethylamide (LSD), hallucinogens, therapeutic use, psychiatric disorders, addiction

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***Correspondence:**
Marta Torrens
mtorrens@parcdesalutmar.cat

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INTRODUCTION

Since its discovery in 1938 by Swiss chemist Albert Hofmann (1), lysergic acid diethylamide (lysergide, LSD) has maintained an unstable relationship with psychiatry. Hofmann synthesized LSD in an effort to develop ergot derivatives with the goal of reducing postpartum hemorrhage. Some years later, after accidentally getting into contact with a small dose, he was the first subject in history to experience its effects (2). At the end of the 1940s, there was great interest among psychiatrist in the potential use of LSD as a therapeutic agent (3), which was actually marketed by Sandoz laboratories under the brand name "Delysid" in the 1950s (4) and used in several psychiatric departments in Europe and America. Even the US Army and CIA experimented with this substance as a truth serum, and LSD was further investigated by the US Army as a potential incapacitating agent, however without success (5). After its prohibition in USA in 1967, due to an increase in popularity and its association with counter-cultural movements, it has taken several decades for a resurgence of interest in its therapeutic potential for psychiatry (6–9).

LSD is part of the pharmacological group known as "classical hallucinogens" or "psychedelics" (term coined by Osmond in 1957) (4), sharing its chemical structure with psilocybin and dimethyltryptamine (DMT) as a variant of indolamine (chemical structure similar to the neurotransmitter serotonin) (10).

The term "classical hallucinogen" is a widely accepted synonym in the literature, with a greater emphasis on the alteration of the perception that these substances cause (11), although its use has been controversial as it does not specify the effect of these agents in consciousness and the self, as indicated by recent psychological and biological studies (12–14). LSD could also be defined, from an anthropological perspective, as an "entheogen", which implies that users experience (mainly in a religious, shamanic or spiritual context) an altered state of consciousness: "as if the eyes had been cleansed and the person could see the world as new in all respects" (15).

Classical hallucinogens are psychoactive substances that are believed to mediate their effects mainly through an agonist activity in the serotonin 2A receptor (5-HT2A) (16). Experimental studies have previously shown that the use of 5-HT2A antagonists attenuate the main effects of these substances, both in rats (17, 18) and human subjects (19–22).

Other receptors which may contribute to the effects of these agents are the serotonin 2C and 1A receptors, as well as other effects in the dopaminergic and noradrenergic system (16). Likewise, these are potent regulators of transcription factors, which could mediate a potential mechanism of action in the synaptic structure with greater persistence of their effects over time (23, 24).

LSD is one of the most potent classical hallucinogens available, with active doses between 0.5 and 2 mcg/kg (100–150 mcg per dose). Its half-life is approximately 3 h, varying between 2 and 5 h, and its psychoactive effects are prolonged over time (up to 12 h depending on the dose, tolerance, weight and age of the subject) (25, 26). Recently LSD has been used in microdoses as low as 10 mcg to enhance performance (27).

The usual mental effects of LSD are distortion of sense of time and identity, alteration in depth and time perception, visual hallucinations, sense of euphoria or certainty, distorted perception of the size and shape of objects, movements, color, sounds, touch and body image and delusions (28).

Concerning safety, the administration of classical hallucinogens carries some risks. One of them is the so-called "bad trip" or "challenging experience", described as an acute state of anxiety, dysphoria and confusion, which can lead to unpredictable behavior in uncontrolled or unsupervised environments (29). Another possible risk is the exacerbation of psychotic disorders or the generation of prolonged psychotic reactions, which could be related to the subject's previous predisposition (30). Although no contemporary study has reported psychosis after the administration of classical hallucinogens, an adequate screening of previous psychotic episodes and the patient's vulnerability is necessary for the use of these substances (31). Another possible adverse effect is a modest increase in blood pressure and heart rate; therefore, patients with severe cardiovascular disease should be excluded from the administration of this agent. Other usual absolute contraindications are pregnancy, epilepsy or paranoid personality traits (32). The remaining adverse effects should not limit its therapeutic use (31, 33).

As a recreational drug, LSD does not entail physical dependence as withdrawal syndrome, as do most of these substances (opioids, cocaine, cannabis and methamphetamine) (34). Its frequent or long-term use can lead to tolerance, and after a single dose, emotional, physical and mental stability is quickly recovered (35, 36). Likewise, classical hallucinogens in general, and LSD in particular, exhibit very low physiological toxicity, even at very high doses, without any evidence of organic damage or neuropsychological deficits (36, 37) associated with their use. Their safety has recently led to considering LSD as one of the safest psychoactive recreational substances (38–42).

However, LSD remains one of the most stigmatized and legally restricted agents among psychoactive substances. It is still included in Schedule I of the United Nations classification of drugs, restricting its use in research and making it difficult to potentially use it as a therapeutic tool in medicine. This classification has recently been questioned by various authors (8, 43). A few decades ago, anecdotal reports of suicidal acts in recreational users were published, and intensely emphasized by the media (44, 45). These attempts are in contrast with some recent population studies, which show significant associations between the use of a single dose of classical hallucinogens and a decrease in the likelihood of psychological distress and suicide (46–48). Other recent studies also established a clear link between life-time use of classical hallucinogens and a lower probability of developing mental problems, as well as a positive association, although non-significant, regarding several variables related to mental health (49, 50). Nevertheless, the unpredictability of subject behavior makes it necessary to

adequately control the environment and monitor the reaction of each individual.

Regarding its therapeutic potential, LSD was used from the 1950s to the 1970s to achieve behavioral and personality changes, as well as remission of psychiatric symptoms in various disorders (30, 51). LSD was used in the treatment of anxiety, depression, psychosomatic diseases and addiction (52). During that time, it was also observed that LSD together with suitable accompaniment during its administration, could reduce pain, anxiety and depression in patients with advanced cancer (53–55) Other studies involving larger patient samples also established its safety and promising results in patients with terminal cancer (56, 57). Studies in schizophrenic patients, however, reached less response to the same dose (58) and worse clinical outcomes (59) compared with non-schizophrenics patients, and negative effects on these patients have been described, both in LSD experience itself and later benefits (60, 61). The data indicate that the responsivity of schizophrenic patients to the administration of lysergic acid is less than that of normal subjects.

Prediction of individual responses to LSD depends on several variables, some of which were already discussed at the international LSD therapy conference in 1965 (52). LSD reaction involves a series of complex interactions between doses, "set" (thoughts, mood and expectations of the subject prior to treatment) and "setting" (the physical and interpersonal environment in which the subject undergoes treatment) (30). Three different major approaches to LSD use as a treatment were then applied to clinical research: "psycholytic therapy", "psychedelic-chemotherapy" and "psychedelic-peak therapy" (62). In psycholytic therapy, mainly practiced in Europe, low-moderate doses (25-200 mcg) of this drug were used in more than one therapeutic session of psychodynamic orientation. In psychedelic-chemotherapy, drug use itself was emphasized at relatively high doses (200 mcg or more), with a very limited or absent psychotherapeutic approach. As for psychedelic-peak therapy (or "psychedelic therapy"), it involves administering a single and relatively high dose with the aim of triggering a mystical-type experience ("peak experience" or "ego dissolution" as synonyms). This approach should include the proper prior preparation of the patient (set) and a comfortable environment during the session (setting), as well as a discussion on it during subsequent follow-up sessions with the subject (after-care related to LSD session) (63). Mystical experiences are referred to as those in which a sense of unity with the environment is experienced achieving a vivid transcendental experience at an emotional, cognitive and ego-structural level, after a previous and personal therapeutic preparation (64). The aim is to catalyze rapid and fundamental changes in the value system and self-image of the subject (65).

Despite the foregoing, most clinical studies involving the use of LSD were published between the 1960s and 1970s, up to the strict prohibition of its use in research. Obviously, most of these studies were not performed under contemporary standards. The purpose of this systematic review is to identify controlled and randomized clinical trials that assess the potential use of LSD in psychiatry and identify variables controlled by the researcher as potentially related to therapeutic outcomes. This is with the aim of informing a discussion on the benefits and challenges of integrating contemporary classic hallucinogens research into modern clinical trial designs and providing a guide for further research involving LSD as a therapeutic agent.

METHODS

Data Acquisition and Search Strategy

This study was conducted according to the requirements established in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols (66).

Pubmed database was searched for the following terms: ["lysergic acid diethylamide" OR "LSD" OR "lysergic acid diethylamide" (MeSH Terms)] OR "lysergic acid") AND ["therapeutics"(MeSH Terms) OR "mental disorder" (MeSH Terms) OR "therapy" OR "psychotherapy" OR "treatment"]. In addition, the Multidisciplinary Association for Psychedelic Studies (MAPS) Psychedelic Bibliography (www.maps.org) was also consulted. To ensure literature saturation, the electronic search was supplemented by a manual review of the reference lists from eligible publications. Two authors independently screened the titles and abstracts yielded by the search against the inclusion criteria. Full reports for all titles that appear to meet the inclusion criteria were obtained. Reviewers resolved disagreements by discussion. The search was limited to the time period compressed between 01-01-1950 and 05-05-2019, based on the results obtained in the reference search.

Search results were examined by two authors (JJF and FF) reading the titles and abstracts. Each potentially relevant publication found during the search was retrieved and assessed for its use in this review after inclusion and exclusion criteria were specified.

Data Items

Dosage, frequency and duration of the treatment, for both experimental and control interventions were extracted. Patient's characteristics (including age, gender and diagnosis) and inclusion/exclusion criteria were extracted together with country, trial design, trial size, and length of follow up. For non-pharmacological comparators, type, frequency and duration of the intervention were extracted, if appropriate.

As studies with different diagnostic groups were included, outcomes varied depending on the psychiatric condition under study. In any case, change scores from baseline or endpoint were extracted. Side effects and overall tolerability were also studied.

Eligibility Criteria

Randomized controlled trials of LSD as a therapeutic tool for psychiatry were included. This review included only randomized controlled clinical trials involving patients with a diagnosis of mental illness. Experimental studies in healthy volunteers were excluded. Trials with no control group or not randomized, animal studies, observational studies, review papers, qualitative studies, case reports, opinion pieces or comments, letters or

editorials, conference abstract, posters and books chapters were excluded. Of interest were interventions using LSD, as a stand-alone treatment or as an adjunctive treatment. Only studies comparing LSD with other interventions were included. Active and non-active comparators were included.

Quality Assessment

The Cochrane Collaboration risk of bias assessment tool was used to determine the quality of the studies (67). This tool involves an assessment of six specific domains: 1) sequence generation, 2) allocation concealment, 3) blinding of participants, 4) personnel and outcome assessors, 5) incomplete outcome data, and 6) selective outcome reporting and other sources of bias. The tool was applied to each RCT independently by two authors. Discrepancies were resolved through discussion with a third author.

RESULTS

A total of 3,668 papers were identified through the search in Pubmed, and 12 additional records were found through other sources (manual search based on review papers and meta-analysis). After the removal of duplicates and exclusion based on titles or abstracts, 43 papers were screened in more detail for eligibility. Subsequently, another 32 were excluded, which resulted in the 11 papers used in this systematic review. This process is described in the PRISMA flowchart (**Figure 1**). The quality of the great majority of the clinical trials found did not conform to modern standards, with a non-randomized control group or without control group itself. The highest quality of trials was observed in studies on the therapeutic use of LSD in alcoholism.

The detailed description of all studies included and their main results can be found in **Tables 1** and **2**.

Place and Publication Date of the Study

Among the selected clinical trials, 3 were carried out in Canada, 7 in the USA and 1 in Switzerland. **Tables 1** and **2** show these clinical trials ordered by date of publication. Note the important 41-year interval between the study by (63); and the modern study by Gasser et al. (75).

Quality Assessment of Studies

A summary of risk of bias is presented in **Table 3**. Based on the definitions provided by the Cochrane risk of bias assessment tool (67), no trials were assessed to show a high risk of bias related to sequence generation, and all trials used random assignment. Moreover, all trials attempted to conceal allocation, but most of them were judged to have unclear risk of allocation concealment (63, 65, 69, 71–73) because did not describe methods in detail.

Five trials (59, 70, 71, 73, 74) were judged to have a high risk of bias due to blinding of patients or staff. In two of them (59, 70), treatment allocation was concealed only until the time of the possible LSD session, and in the other three trials (71, 73, 74) no attempt of blindness or to single blind was made or designed. The rest of them (62, 65, 68, 69, 72, 75) used double-blind designs with active placebo, but in "Smart et al." blinding of one of the two control groups (control group without active placebo) was not explicitly described.

All trials were judged to have low or an unclear risk of bias due to independent and blind assessment. In one

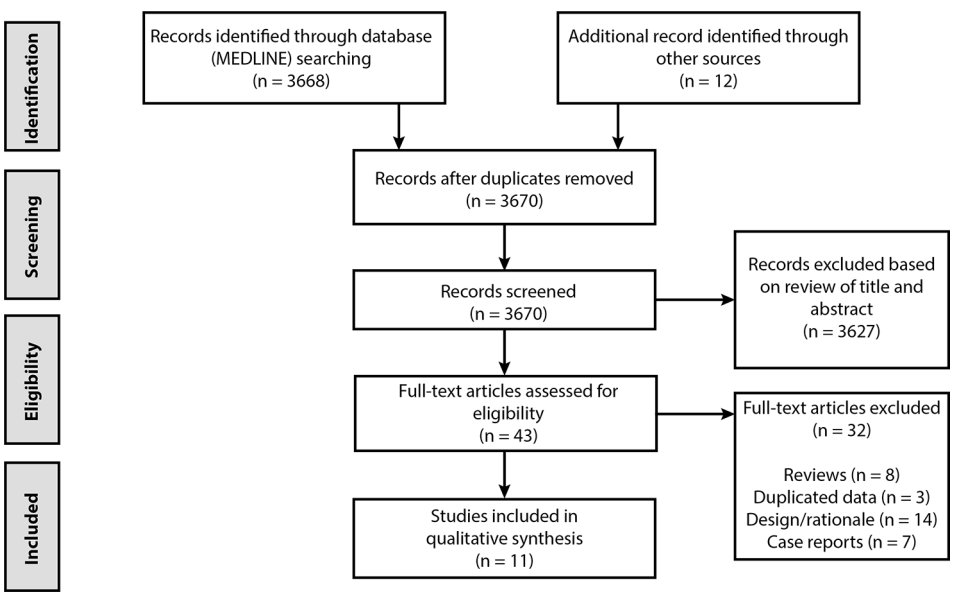

FIGURE 1 | PRISMA flowchart of selected abstracts and articles.

TABLE 1 | Details of studies: design, diagnosis and measurement.

Clinical Trial; (Country)	LSD dosage (n)	Control (n)	Blinding	Target condition/ Inclusion criteria	Measures (time horizon)
Smart et al. (68); (Canada)	800 mcg (10)	60 mg ephedrine sulfate (10) No drug (10)	Double-blind (not to "no drug" group) Independent assessors	Alcoholics, "long history of excessive and uncontrolled drinking" (Male and female)	Drinking History Questionnaire, Abstinence (6 months) Maudsley personality inventory, Haigh-Butler Q, Rorschach, Wechsler Adult Intellingence Scale
Hollister et al. (69); (USA)	600 mcg (36)	60 mg d-amphetamine (36)	Double blind Independent assessors	Alcoholic Veterans, "acute alcoholic episode within 2 weeks of admission; all problem drinkers" (Male)	Drinking Behaviour Scale (2, 6 months)
Ludwig et al. (70); (USA)	3 mcg/kg 210 mcg mean (132)	No drug (44)	Double blind until LSD session Independent assessors	Alcoholics, "up to 4 previous admissions for treatment of alcoholism" (Male)	Behaviour Rating Scale (6, 12 months) Abstinence (1, 3 months) California Psychological Inventory
Johnson (71); (Canada)	300 mcg initial dose + 264 mcg mean (48)	3.75 g Sodium Amytal + 30 mg Methedrine (22) / No drug (25)	Single blind Independent assessors	Alcoholics in outpatient treatment (Male and female)	Abstinence, Drinking practice/consequences (12 months) Differential Personality Inventory, Quick test, Hidden Figures test
Bowen et al. (72); (USA)	500 mcg (22)	25 mcg LSD (22) No drug (15)	Double-blind Independent assessors not mentioned	Alcoholic Veterans under voluntary treatment for alcoholism (Male)	Adjustment scale (12 months)
Denson and Sydiaha (73); (Canada)	50-300 mcg (163 mean) in subsequent dosage + 5 mg dextroamphetamine prior to LSD (25)	No drug (26)	No attempt of blind Independent assessors	Alcoholic and neurotic patients (Male and female)	Eysenck Personality Inventory, IPAT Objective Anxiety Scale, Minnesota Multiphasic Personality Inventory, Lorr Multi-dimensional Rating Scale, Background Questionnaire for Non-Schizophrenic Patients (BFQNSP) (6, 12 months)
Pahnke et al. (62); (USA)	450 mcg (73)	50 mcg LSD (44)	Double-blind Independent assessors	Alcoholics under voluntary treatment for alcoholism (Male)	Drinking Behaviour Scale, Global Adjustment (6 months)
Tomsovic and Edwards (59); (USA)	500 mcg (32) *non-schizophrenics	Usual treatment (45) *non-schizophrenics	Double-blind until LSD sesión Self-report assessment	Alcoholics with 12 years average of problem drinking (Male)	Drinking Adjustment Scale (3, 6, 12 months) Blewett and Chwelos Scales
Savage and McCabe (74); (USA)	300-450 mcg (37)	Usual treatment (37)	No attempt of blind Independent assessors	Narcotic addicts in Maryland correctional institutions (Male)	Global adjustment rating scale, Abstinence (6, 12 months)
Savage et al. (65); (USA)	350 mcg (31)	50 mcg LSD (32) Usual treatment (33)	Double-blind Independent assessors	Patients with psychoneurotic diagnosis, "depressed and anxious" (Male and female)	Psychiatric evaluation profile, Katz Adjustment Scale, Global adjustment scale (6 months) Block Design, Digit Span, Digit Symbol, Progressive Matrices, Embedded Figures, Benton Visual Retention Test, Minnesota Multiphasic Personality Inventory, Eysenck Personality Inventory, Personal Orientation Inventory
Gasser et al. (75); (Switzerland)	200 mcg (8)	20 mcg LSD (3)	Double blind Independent assessors	Anxiety associated with life- threatening deseases patients (Male and female)	State-Trait Anxiety Inventory, European Cancer Quality of Life Questionnaire, SCL-90-R, Hospital Anxiety and Depression Scale, (1 week, 2, 12 months)

trial (72) the outcome assessor was not explicitly described as allocation-blind and in another one (59) the assessment was collected by self-report questionnaire, confirmed by telephone interview with a close relative or friend. The rest of them (62, 65, 68–71, 74, 75) had independent and allocation-blind assessors.

Two trials (62, 72) were judged to have a high risk of bias due to incomplete outcome data, because participants were excluded

TABLE 2 | Details of studies: set, setting and main findings.

Clinical Trial; (Country)	Treatment program	Pre-LSD session	LSD session	Setting	Main findings
Smart et al. (68); (Canada)	Therapeutic community (group and individual therapy)	Brief orientation	3h interview and no full-time observation	Waist belt to bed No music/visual stimuli	Improvement in total abstinence/ longest period of abstinence for all groups No significant differences between groups
Hollister et al. (69); (USA)	Short therapy on alcohol withdrawal (7 days)	Brief orientation	Brief supportive reassurance (focus on the self)	Music stimuli Visual stimuli (comfortable furniture)	Significant improvement for LSD group (2 months) in Drinking Behavior Scale scores No significant differences at 6 months
Ludwig et al. (70); (USA)	Intensive milieu therapy (30 days) Group therapy	Brief orientation	3h of therapy (psychedelic therapy (44) hypnodelic therapy (44), or silent observation (44))	Not described	Significant improvement in pre-post treatment evaluation for all groups Significant improvement in BRS for all groups in every period No significant differences between groups
Johnson (71); (Canada)	Milieu therapy (24h hospitalization)	Brief orientation	4h of therapy (active interviewing to focus particularly on current problems)	Waist belt to bed No music/visual stimuli	Significant improvement across all groups on most drinking indices No significant differences between groups
Bowen et al. (72); (USA)	Group therapy (60 days)	Group lectures on possible drug effects	Supportive reassurance (focused particularly on non-verbal introspection)	Music stimuli Visual stimuli (flowers, pictures, "tasteful furniture", mirror)	No significant differences between groups at 1 year after LSD session.
Denson and Sydiaha (73); (Canada)	Not described (24 h)	Not reported	Not described	Not described (general hospital setting)	Positive results in general health (BFQNSP) for LSD group No other significant differences
Pahnke et al. (62); (Canada)	Intensive individual therapy (49 days)	Extensive individual preparation for treatment	Therapy for eliciting a "peak or transcendental experience"	Music stimuli Visual stimuli (flowers, pictures, "comfortable living room")	Significant improvement in Global Adjustment and Drinking Behavior for LSD group Significant relationship between better Global Adjustment and peak-experiences
Tomsovic and Edwards (59); (Canada)	Group therapy (90 days)	Lectures and reviews of treatment intentions	Supportive reassurance (not focused on extensive talking)	Music stimuli Visual stimuli (flowers, colorful drapes, pictures, hand mirror, scenic view)	Improvement in abstinence for LSD group (significant for control sub-group 1) No differences between lysergide experience measures and benefit
Savage and McCabe (74); (USA)	Brief residential psychedelic psychotherapy (4-6 weeks) in outpatient clinic program	Preparatory psychotherapy (24 h) focused on positive patient-therapist relationship	Psychedelic therapy	Not described	Significant improvement in total abstinence for LSD group Not significant differences in global adjustment scale
Savage et al. (65); (USA)	Brief hospitalization, psychedelic psychotherapy (4-8 weeks)	Preparation based on the psychedelic model of psychotherapy (3-5 weeks)	Psychedelic therapy	Not described	Significant improvement in majority of pre-post-treatment measures for LSD group Not significant differences between groups at 6 months
Gasser et al. (75); (Switzerland)	Continuous psychotherapeutic process lasting several months (outpatient program)	Two preparatory psychotherapy sessions "Set", based on the psychedelic model of psychotherapy	Psychedelic therapy	Music stimuli Visual stimuli not described "Safe, quiet and pleasant room"	Significant improvement in State-Trait Anxiety Inventory (STAI) scores for LSD group at 2 months Positive trends in reductions in trait anxiety (STAI) at 2 months STAI reductions sustained for 12 months

if they did not complete the intended treatment program (72) or if received additional doses of LSD (62).

Four studies (59, 65, 69, 73) had substantial rates of missing participants at follow-up. However, retention rates were generally high, and data missed in one of the trials (63) was only representative at 12 and 18 months, not at 6 months. In the other three trials (59, 69, 73), authors considered missing participants as unimproved.

Three trials (69, 70, 73) were judged to have a high risk of bias because of possible selective outcome reporting, presenting lack

TABLE 3 | Quality assessment of all included studies based on the risk of bias.

Clinical trial	Random sequence generation	Allocation concealment	Blinding for participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Smart et al. (68)	Low	Low	Unclear	Low	Low	Low	Low
Hollister et al. (69)	Low	Unclear	Low	Low	Low	High	Low
Ludwig et al. (70)	Low	Unclear	High	Low	Low	High	Low
Hollister et al. (69)	Low	Unclear	High	Low	Unclear	Unclear	High
Bowen et al. (72)	Low	Low	Low	Unclear	High	Low	Low
Johnson (71)	Low	Unclear	High	Unclear	Unclear	High	Unclear
Pahnke et al. (62)	Low	Unclear	Low	Low	High	Low	High
Tomsovic and Edwards (59)	Low	Low	High	Unclear	Low	Low	Low
Savage and McCabe (74)	Low	Low	High	Low	Low	Low	High
Savage et al. (70)	Low	Unclear	Low	Low	Low	Low	High
Gasser et al. (75)	Low	Low	Low	Low	Low	Low	Unclear

of clarity at short-term follow-up clinical outcome and giving more detailed data at medium or late-term follow-up. Another trial (71) was judged to have an unclear risk because some measures were not strictly reported.

Finally, four trials (62, 65, 71, 74) were judged to have a high risk of other sources of bias. In one of them (62), due to baseline imbalance (full-dose LSD participants were less likely to be divorced and more likely to have prior admissions for alcohol treatment), other trial (65) due to treatment time (full-dose LSD participants were more likely to have more psychotherapy hours) and the rest of them (71, 74) due to a shorter time of hospitalization [from one day (71) to a few days (74)] for the LSD treatment group and not the control group. Two last trials (73, 75) presented unclear risk of bias due to uneven concurrent use of other pharmacological treatments during study between participants.

LSD Dosage and Method

LSD was administered to 567 patients in a dose range from 20 to 800 mcg. The oral route was significantly the most used one, while one study (71) used the intravenous route and another one (68) did not describe the route used. A single dose of LSD was the procedure of choice for most selected clinical trials. Other studies (71, 73) opted for a dosage-escalation approach, and some (73, 75) offered the possibility of repeating LSD doses at 2–3 week intervals.

The concomitant use in some of the studies of other pharmacological principles, such as dextroamphetamine (73) prior to the dose of LSD, or chlorpromazine or promazine (71, 73) after LSD treatment is worth mentioning. Since the therapeutic potential of LSD may be underestimated or masked by such treatments.

Safety and Adverse Effects

Most studies describe exclusion criteria for patients to be treated with LSD. Severe organic disease (mainly at neurological and cardiovascular levels) was a common exclusion criteria (63, 66–69).

"Gasser et al." do not rule out those patients with cardiovascular disease, due to the idiosyncrasy of subjects under study (life-threatening diseases). Two of the studies (67, 75) also excluded those patients with a history of severe affective disorder. Most clinical trials (65, 68–71, 74, 75) discarded those patients with active psychosis for the study, but some of them (65, 68, 70, 74) did not rule out patients with a history of psychosis in the past. It is noteworthy that in the study of Tomsovic and Edwards (59), LSD was administered to a subgroup of 12 patients diagnosed with schizophrenia (withdrawn from **Table 1**, due to modern exclusion criteria), to which they applied a separate statistical analysis that showed better results for the subgroup of non- schizophrenics who had received a single LSD dose.

Two cases of serious adverse effects were reported. In one of the studies (69), authors described a tonic–clonic seizure, without subsequent complications, in a patient with a previous history of seizures in a context of abstinent clinical symptoms. In another one (74), a case of prolonged psychosis was reported in a 21-year-old patient with a previous history of recurrent psychotic episodes in the context of hospitalization during adolescence. This patient received psychotherapy and antipsychotic medication, recovering without later complications. No other serious adverse effects were described in the remaining 565 subjects.

Control Group and Active Placebo

Five studies within our review (68, 70–73) designed a control group for which no drug was administered, and three others (59, 65, 76) had a control group in which the usual treatment was applied to patients during hospitalization. In "Savage et al." the control group had the added benefit of participating in one hour and a half group therapy sessions three times a week, which were defined as eclectic (focused on the solution of specific problems through group interaction). Most studies (see **Table 1**) had a control group in which active placebo was used, and four of them (62, 65, 72, 75) used LSD itself at a lower dose. The difficulty in maintaining patient and therapist uncertainty, even with active placebo, is underlined by authors. With ephedrine sulfate (68), in 19 of 20 cases the therapist correctly guessed which type of drug was administered to the patient, and 20 mcg of LSD (75) was considered too low a dose

to avoid unmasking the control group, both for patient and therapist.

Treatment Program and "Set"

There was great heterogeneity among the clinical trials chosen for this review in terms of patient preparation and the general therapeutic program to which LSD treatment was added. **Table 2** shows the type of treatment program used in each study, ranging from 24 h to 90 days from the start of treatment to patient discharge. The treatment program between different studies also differed in structure, varying between highly structured intensive programs (70) (with five weekly meetings, seminars, group and individual therapy, occupational therapy and rehabilitation program) and the absence (73) of a specific program.

Preparation of the subject for LSD treatment ranged from very brief orientation (68–71 to extensive preparation (62, 65, 74, 75) with the aim of promoting the therapeutic experience. Preparation time (pre-LSD session, **Table 2**), ranged from a few hours to 5 weeks. The only information provided to subjects in some cases was the great variation in the individual response of the drug (68), or very brief data on the nature of response (69), with no intention to perform previous therapy. One of these authors (70) points out that the previous preparation of patients to LSD administration was possibly insufficient for achieving therapeutic objectives.

Despite heterogeneity, there was a trend among most modern trials within our review to emphasize the importance of the "set" of the subjects to be studied, devoting more time and providing them with a structure. In the earliest study meeting these characteristics (72), patients were previously informed of the nature of the drug, stating whether they would receive a small or a large dose. Within the LSD group of treatment (full-dose or active placebo), approximately half of the patients performed the session during the first 3 weeks, with the remaining subjects receiving LSD treatment during the last 3 weeks. There was a non-significant trend towards better results among those who received treatment during the last 3 weeks, which was highlighted by the authors as a positive association between "set" and therapeutic outcomes.

Therapeutic Approach and "Setting"

Therapeutic Approach

Again, great heterogeneity was observed among studies regarding the therapeutic approach during the treatment with LSD. Two studies (68, 71) applied an approach based on active and directed interviews focused on problems derived from alcohol dependence. In one of these trials (68), these interviews were described as an attempt to discover alternatives to alcohol use, and to define patient attitudes regarding the transfer with the therapist, the act of moving towards drinking, parental relationships, suicidal ideation or sexual behavior.

In three of the studies (59, 69, 72), no psychotherapy attempts were made during the treatment session. In one of them (69), an effort was made to maintain a supportive environment, which included non-verbal communication. In another study (70), three different approaches were used during the LSD session, defined as "psychedelic therapy", "hypnodelic therapy" and "silent observation", to study possible differences in their therapeutic potential. The author described "an active, dynamically oriented psychotherapy, with the primary focus on major problem areas", which contrast with the description of "psychedelic therapy" considered above. The most common approach among these studies (62, 65, 74, 75) was to use psychedelic therapy, defined as 12-14 h after one relatively high LSD dose (200-500 mcg), during which a nurse and a therapist provide constant attention (65) with the aim of the subject achieving a "peak or transcendental experience" (62).

Setting

Regarding the physical (sensory stimuli) and interpersonal environment of subjects during the LSD treatment (see **Table 2**), in five trials (59, 62, 69, 72, 75), musical stimulation during the session was offered. Descriptions of environment were varied, finding "comfortable or tastefull furniture" (62, 69, 72) or "flowers and pictures" (59, 62) as examples. In four of the studies (65, 70, 73, 74), the physical environment was not described. Likewise, in two studies (66, 69), the use of waist belt to bed method was mentioned to prevent subjects from leaving their position. Regarding the interpersonal environment, the fact that in the earliest study (68) subjects were unaccompanied for an indefinite period of time during the treatment is noteworthy.

Efficacy

The efficacy of the intervention with LSD was presented by the main diagnosis where the substance was administered.

Alcohol Use Disorder

Most clinical trials in this review (59, 62, 68–73) evaluated the therapeutic potential of LSD in the treatment of alcohol use disorder. The main outcomes of these studies and their main statistical analysis were summarized below, by order of publication.

In the study by "Smart et al." there was a substantial improvement in abstinence (total abstinence and longest period of abstinence) in all three groups [LSD group (800 mcg), active placebo group (60 mg ephedrine sulfate) and "no drug" group], but no significant differences were found between them (ANOVA, $p > 0.05$). There were no significant differences between groups either in the Drinking History Questionnaire nor in number of voluntary contacts with the clinic afterwards.

The second study (69) showed a significant improvement (t-test, $p < 0.01$) in the 2-month follow-up in the LSD group with respect to dextroamphetamine, based on the Drinking Behavior Scale score. No significant differences were found at 6 months follow-up, except for two specific symptoms of this scale (related to work performance), in which LSD was shown to be superior to dextroamphetamine (chi-square, $p < 0.05$).

Conversely, in the study by "Ludwig et al.", results showed a significant improvement at two weeks of treatment (t-test for correlated means, $p < 0.05$) for all four groups (three different approaches in LSD group (Hypnodelic therapy group, Psychedelic therapy group and Silent Observation group) and control group). However, no significant differences were found

between them (ANCOVA, no alpha value reported). In the same way, a significant improvement (t-test for correlated means, $p < 0.05$) was observed in the Behavior Rating Scale values for each period (6, 12 months) in all groups, without finding significant differences (ANCOVA, no alpha value reported) between them.

In the next study (71), a significant improvement was found in terms of abstinence (ANOVA, $p < 0.01$), drinking behavior (ANOVA, $p < 0.01$) and employment rate (ANOVA, $p < 0.05$) after treatment in all groups (LSD treatment group, active placebo (Sodium Amytal and Methedrine) control group, and "no drug" control group). However, no significant differences (chi-square, $p > 0.05$) were found between them. In the same direction, in the study by "Bowen et al.", no significant differences were found between groups (chi-square, $p > 0.05$).

In the study by "Denson et al.", no significant differences (chi-square, $p > 0.05$) were observed between groups (LSD group and control group) at follow-up, except in the Background and Follow-up Questionnaire for Non-Schizophrenic Patients (BFQNSP) data, in which the LSD treatment group showed better results in terms of general health (chi-square, $p < 0.05$).

In the next study (62), significant improvements were observed in Global Adjustment (ANCOVA, $p < 0.05$) and Drinking Behavior (ANCOVA, $p < 0.025$) for the LSD treatment group compared to the control group at 6 months.

Finally, in the last trial (59), a higher percentage of abstinence was observed among the LSD treatment group compared to the remaining groups (control group 1: no treatment, only ongoing follow-up evaluation; control group 2: usual treatment, "Regular Alcoholic Rehabilitation Program") at three months, maintaining this superiority at one year in several grades. A statistical difference (chi-square $p < 0.01$) was observed between the LSD group and the control group 1, but authors emphasized that the control group 1 was not representative of the best results observed in the control group 2.

In summary, it was observed a significant effect of LSD in four studies performed. However, this effect was related to quality of life and general health in some of the studies, with no clear improvements in alcohol abstinence.

Neurotic Symptoms (Anxiety, Depression, and Psychosomatic Diseases)

Two trials (65, 73) evaluated LSD as a treatment of neurotic symptoms. This diagnosis was referred to as depressive neurosis, obsessive-compulsive reaction, phobic reaction, anxiety state, hysteria, psychoneurosis with somatic symptoms, character disorder and sexual neurosis. The presence of all symptomatology was not required, and a subset of neurotic symptoms was adequate. "Denson et al." found significant differences (chi-square, $p < 0.05$) in Questionnaire data (BFQNSP), in which the LSD treatment group showed better results in terms of general health at 6 and 12 months. Also, in the study by "Savage et al.", a significant improvement (chi-square, $p < 0.05$) was observed at 6-8 weeks in most of measurements used for all three groups (LSD treatment group, active placebo (LSD) control group and "usual treatment" control group). This improvement (mainly focused on symptomatology and self-actualization) was significantly greater as an average for the LSD treatment group compared to the "usual treatment" control group, as well as for some measurements used for the active placebo (LSD) control group compared to the "usual treatment" control group. The LSD treatment group showed superiority (chi-square, $p < 0.05$) with respect to both control groups in a sub-scale of the Minnesota Multiphasic Personality Inventory (F scale, focused on general psychopathology). Regarding subsequent evaluation (6 months), all groups showed significant differences in a large number of variables, but in this case the results of the statistical analysis failed to reach the defined significance level (ANCOVA, $p > 0.05$) between the groups.

Heroin Use Disorder

Only one study (74) met the inclusion criteria in our review. Significant differences were observed (chi square, $p < 0.05$) in total abstinence rates in favor of the LSD treatment group at 12 months. A trend, not statistically significant (chi-square, $p < 0.02$), was observed in favor of the LSD treatment group in Global Adjustment Rating Scale.

Anxiety Associated With Life-Threatening Diseases

A modern study (75) assessed anxiety associated with chronic inflammatory disease, chronic motor disease and cancer. All patients had a score of 40 and above in the State-Trait Anxiety Inventory (STAI). A positive tendency in trait anxiety reduction (ANOVA, $p = 0.033$) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, $p = 0.021$) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group, however with no significant difference (ANOVA, $p > 0.05$).

Aftercare Related to Experimental (LSD) Sessions

In some studies (69, 73) patients could be discharged after 24 h or in less time (73) if they were able to be assisted by friends or relatives. Other studies did not specify which patients maintained subsequent therapy (70), or did not examine session results unless patients actively requested it (68). In one of these studies (70), a possibly inadequate follow-up of subjects was mentioned, without giving them the opportunity to receive further treatment.

One of the authors (72) suggested that short-term changes that occurred frequently in subjects' personality could be integrated and applied to their daily-life insight with greater support and additional help after hospital discharge. In one study (65), patients remained hospitalized at least one week after the LSD session, being visited by their therapists repeatedly. In this study, a second session with LSD was offered to those patients who were considered suitable for second exposure (approximately 25% out of both LSD groups (full-dose and active placebo) received an equal second dose). In another study (75), a second dose was also offered to subjects in the

active placebo group at months of follow-up (open- label cross-over design). Finally, in one of trials (70), half of each group was also treated with disulfiram (daily dose of 500 mg) after hospital discharge. Patients were strongly encouraged to take a fixed, prescribed dosage every day, instructed on the dangers of imbibing alcohol while on disulfiram, and started on the drug four days prior to hospital discharge. They were given a six-month supply of disulfiram and instructed to take one 500 mg tablet per day. Baseline to post-treatment t-tests revealed significant improvement (t-test for correlated means, $p < 0.05$) in Behavior Rating Scale for every group at every period, while two-way analysis of covariance revealed no significant differences (ANCOVA, no alpha value reported) between groups that received disulfiram and those that did not after hospital discharge, for any of the measurements studied.

Variables in Therapeutic Response

Some studies (59, 62, 74) described efforts to predict therapeutic outcomes in relation to an acute hallucinogen experience. In one of them (59), it was emphasized that the methodology used did not manage to measure crucial aspects of the experience that foresee subsequent benefits. In two others, a significant link was observed between values in the Global Adjustment Scale (62) and the probability of optimal adjustment in the community (74) in relation to the achievement of a "mystical or peak experience" during the LSD session. One of these authors (62) identified the LSD dose as a better predictor than the type of experience in his study; although he also pointed out that there was a close link between "peak-experiences" and a higher drug dose.

On the other hand, in two studies (59, 74) it was observed that patients who seemed to benefit from the treatment with LSD did so optimally with more probability. A greater likelihood of complete abstinence from alcohol (59) or optimal adjustment in the community (74) was observed after the LSD treatment.

Finally, one of the authors (65) highlighted that male patients showed a clear improvement in Global Adjustment with as full dose (350 mcg) of LSD at six months post ingestion, while in females, a greater improvement was observed with low doses of 50 mcg (ANCOVA, $p < 0.1$).

DISCUSSION

Despite design heterogeneity among the clinical trials in this review, some positive results were observed, revealing the therapeutic potential of LSD in the reduction of psychiatric symptomatology. The vast majority of authors described important positive short-term changes in patients, although in some studies (59, 65, 69) an important homogenization was observed between the LSD treatment group and the control group at long-term follow-up. Some previous studies of lower quality (77) also exemplified a clear improvement in short-term adjustment, with a later tendency to balance results with the control group. However, this is in contrast with the results shown by some authors (62, 74, 75), in which therapeutic changes were maintained at 6–12 months after treatment. Moreover, in a follow-up study (78) beneficial changes were found at one year of follow-up for hallucinogen therapy compared with conventional psychotherapy in adolescent behavior disorders. Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed positive effects more than a year after a LSD or psilocybin single dose (79, 80).

The results of this review could conclude that alcohol use disorder patients may benefit from LSD treatment. Other studies with a lower quality control group (patients did not receive a treatment comparable to the treatment group) also found significant differences in favor of LSD treatment in alcoholism (60, 81). Likewise, according to a retrospective analysis of studies published in the late 1960s, LSD is a potential therapeutic agent for the treatment of chronic alcoholism (82). A recent meta-analysis (83) of six of the clinical trials chosen for this review showed the superiority of LSD over placebo in the treatment of alcoholism with an odds ratio (OR) of 1.96 (95% confidence interval 1.36–2.84 OR, $p = 0.0003$). This study found that a LSD single dose was comparable in terms of effectiveness with the daily intake of naltrexone, acamprosate, or disulfiram in alcoholism treatment (84–86). Other studies in our review also found promising results regarding LSD use for the treatment of heroin use disorder, anxiety, depression, psychosomatic illnesses, and anxiety in relation to life-threatening diseases. Regarding the latter, several authors (56, 57) emphasize the difficulty of designing placebo-controlled and double-blind trials, due to ethical reasons and the nature of the psychoactive intervention.

Regarding the disparity between some results in our review, and as noted by Pahnke et al. (62) "it is essential to keep in mind the differences in procedure among the various methods, not only because of different kinds of experiences being facilitated, but also because of conflicting results that can be correlated with the method used". LSD invariably involves a complex interaction between drug dosage, set and setting. This link is also objectified in different studies, showing the significant relationship between the therapeutic efficacy of hallucinogens and an adequate set, setting and integration of later experience (62, 87–90). This could explain some differences between the results of these reviewed trials, in which there was a great variation between the approach of "Smart et al.", (Psychedelic–chemotherapy: no attempt of psychotherapy, waist belt) and that of "Savage et al." (psychedelic therapy: set, setting and aftercare related to the LSD session). Some authors (91) argued that the accepted methods proven to generate some beneficial experience with LSD are far from those used by Smart at the 1960s. Therefore, the inherent difficulty in conducting a double blind controlled clinical trials with LSD should be mentioned. In 1964, Whitaker (92) stated his opposition to the design of a control group with this type of substance, due to the promising responses of first patients as opposed to the control group. Due to this difficulty, widely discussed at the time, many studies previous to that carried out by "Smart et al.", did not apply adequate measures or assessments, without a control group or properly designed statistical analysis. In this regard, Tomsovic and

Edwards (59) mentioned "the complexities and difficulties of achieving control over the placebo effect of a drug that has spectacular mind-altering properties, and where research is contaminated by expectations of benefit".

Also, modern clinical trials are currently facing a series of problems, which could be summarized as follows (93). Firstly, subjective and objective changes experienced with LSD and the rest of hallucinogens, apparent for both the subject and observer, make performing double-blind tests virtually impossible. Likewise, adequate placebo control becomes extremely difficult due to the absence of such changes in the control group. Strict control of the variables related to the therapeutic benefits of LSD is also necessary. Finally, research with these substances must overcome a series of strict ethical committees and restrictions at the legal level.

When attempting to solve difficulties in terms of blinding and adequate placebo control, a valid approach is an active placebo, using LSD at lower doses (94), an approach already suggested within some of clinical trials in our review (62, 65). This methodology, despite possibly minimizing the effects of LSD when compared to its sole administration, is based on results by numerous researchers who have observed the link between dose and quality and intensity of the hallucinogen response (95–98). Dosage and form of administration, as well as the context in which it is carried out, can be strictly controlled within a hospital setting. The possible effects of microdoses of LSD must be takin into account, possibly limiting its use.

Despite the known unpredictability of hallucinogens, great efforts have been made in recent years to know which variables are associated with the therapeutic value of these substances, finding mystical-type experiences as one of the objectives to be achieved (97, 99, 100). Results of recent investigations show that mystical-type experiences are associated with positive long-term changes after a dose of hallucinogens (33, 79, 99–102). The musical stimuli variable has also been observed as a predictor of mystical-type experiences and positive therapy outcomes (103).

As noted by Gasser (76), designing qualitative studies, not only based on pathology-oriented measurements, is also important to detect variables related to other psychopathological symptoms that can potentially be improved by LSD use (e.g. equanimity, self- assurance and mental strength). Currently, there are validated scales available to measure the quality of the hallucinogen experience, such as the Mystical Experience Questionnaire (MEQ-30) (104) and the Ego-Dissolution Inventory (EDI) (96). The apparently unpredictable nature of these experiences makes studying them in empirical research equally difficult and necessary (14, 104, 105).

Moreover, numerous recent studies with LSD regarding changes in neural networks have been carried out. Modularity and integration networks (as observed in resting- state functional connectivity) have been shown to decrease due to effects of LSD (106, 107). Patterns compared to normal waking consciousness have been demonstrated with LSD (108), and a correlation between subjective reports of "ego dissolution" during LSD and an increment of the overall connectivity and global integration of the brain was found (109). These changes at the cerebral level during the acute effects of hallucinogens have been associated with the aforementioned subjective effects "ego dissolution" and "mystical-type", and could be related to the wide therapeutic value of these substances (101, 102, 105, 110).

Likewise, multiple modern clinical trials involving other hallucinogens have been carried out in the last decade, mainly with psilocybin. Hopeful results have been found for the treatment of alcohol (111) or tobacco (112) addiction, anxiety in relation to advanced cancer (113) or obsessive-compulsive disorder (114). Moderate doses of psilocybin (200 μg/kg) have been used in some modern studies, either with dose escalation (114) or the same dose in various sessions (113), something reminiscent of the psycholithic therapy used in Europe in the past century. Some possible reasons for the greater use of psilocybin over LSD in modern trials were the shorter duration of one effects of the former (thus avoiding hospitalization) or the greater stigma that prevailed regarding the latter (making it difficult to get economic funds and the approval by ethical committees). Beyond psychiatry, the therapeutic potential of LSD in other medicine fields has recently become evident, as in the treatment of cluster headaches in neurology (115).

As it has been previously pointed out, the homogenization of the therapeutic approach is strictly necessary, and training programs related to research and psychotherapy with hallucinogens have recently been developed (116). Also, there are modern guidelines available for the correct use of hallucinogens in clinical research (31). Therefore, the reborn interest of the therapeutic potential of hallucinogens in modern clinical trials is evident, something proven by the remarkable increase in the number of studies carried out with these substances over the last decade (117).

The present review has limitations. Firstly, only articles written in English were selected; this could imply that articles in other languages were excluded despite the fact that these might have provided valuable information. Furthermore, as mentioned above, most studies were carried out during the past century. Moreover and as previously discussed, there was considerable heterogeneity in their design. Also, differences regarding patient populations, features, and diagnostic methods were noticed. Therefore, due to the lack of studies and the features exhibited by selected research, this review can contribute limited evidence on the topic of interest.

This study comes with its own set of strengths. On the one hand, to our knowledge this is the first systematic review of randomized-controlled trials to assess the therapeutic potential of LSD in psychiatry. On the other, a strict selection of studies was carried out, considering inclusion and exclusion criteria as well as confounding factors. With regards to this and in spite of the heterogeneity mentioned above, the important therapeutic value of LSD is revealed and it is observed to be related to variables controlled by the researcher, such as: set, setting and aftercare related to the LSD session. Another positive aspect of this review is that our results highlight the need for randomized-controlled clinical trials with standardized methods to accurately assess the quality of an acute hallucinogen experience. Finally,

this review could serve as a guide for further research involving LSD as a therapeutic agent.

CONCLUSIONS

In conclusion, and despite some controversial results mentioned above, LSD is revealed as a potential therapeutic agent in psychiatry; the evidence to date is strongest for the use of LSD in the treatment of alcoholism. Despite the difficulty of designing double-blind clinical trials with this substance, new studies performed under modern standards are necessary in order to strengthen our knowledge, help erase the stigma that still prevails around these substances and open new doors in the future.

AUTHOR CONTRIBUTIONS

JF, FF, ME, MF, and MT designed the review. JF and FF reviewed the abstracts and the papers. JF and ME obtained the data from the selected articles. JF, FF, ME, MF, and MT wrote and reviewed the manuscript.

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Persisting Reductions in Cannabis, Opioid, and Stimulant Misuse After Naturalistic Psychedelic Use: An Online Survey

Albert Garcia-Romeu[1], *Alan K. Davis*[1,2], *Earth Erowid*[3], *Fire Erowid*[3], *Roland R. Griffiths*[1,4] *and Matthew W. Johnson*[1]*

[1] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2] College of Social Work, The Ohio State University, Columbus, OH, United States, [3] Erowid Center, Grass Valley, CA, United States, [4] Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, United States

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***Correspondence:**
Matthew W. Johnson
mwj@jhu.edu

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Background: Observational data and preliminary studies suggest serotonin 2A agonist psychedelics may hold potential in treating a variety of substance use disorders (SUDs), including opioid use disorder (OUD).

Aims: The study aim was to describe and analyze self-reported cases in which naturalistic psychedelic use was followed by cessation or reduction in other substance use.

Methods: An anonymous online survey of individuals reporting cessation or reduction in cannabis, opioid, or stimulant use following psychedelic use in non-clinical settings.

Results: Four hundred forty-four respondents, mostly in the USA (67%) completed the survey. Participants reported 4.5 years of problematic substance use on average before the psychedelic experience to which they attributed a reduction in drug consumption, with 79% meeting retrospective criteria for severe SUD. Most reported taking a moderate or high dose of LSD (43%) or psilocybin-containing mushrooms (29%), followed by significant reduction in drug consumption. Before the psychedelic experience 96% met SUD criteria, whereas only 27% met SUD criteria afterward. Participants rated their psychedelic experience as highly meaningful and insightful, with 28% endorsing psychedelic-associated changes in life priorities or values as facilitating reduced substance misuse. Greater psychedelic dose, insight, mystical-type effects, and personal meaning of experiences were associated with greater reduction in drug consumption.

Conclusions: While these cross-sectional and self-report methods cannot determine whether psychedelics caused changes in drug use, results suggest the potential that psychedelics cause reductions in problematic substance use, and support additional clinical research on psychedelic-assisted treatment for SUD.

Keywords: psychedelics, hallucinogens, psilocybin, lysergic acid diethylamide (LSD), addiction, opioid, cannabis, stimulant

INTRODUCTION

Substance misuse is a leading preventable cause of morbidity and mortality (1, 2), and contributed to over 63,000 drug overdose deaths in the US in 2016 (3). An estimated 23.3 million Americans have met *Diagnostic and Statistical Manual of Mental Disorders 5th Ed.* (DSM-5; 4) criteria for a substance use disorder (SUD) regarding a drug besides alcohol or tobacco in their lifetime (5). Cannabis, opioids, and cocaine constitute the greatest proportion of these diagnoses (5). Recent trends have shown increased adult use of cannabis (6–8), opioids (9–11), and stimulant drugs (12, 13), and associated adverse public health outcomes (3).

Though cannabis use among those age 12–17 has largely decreased in recent years (6, 14), adults have shown greater use as more states have approved medical or recreational accessibility (8, 15). Concurrently, cannabis related emergency room visits (16) and prevalence of cannabis use disorder have risen (8). The United States has recently seen unprecedented levels of opioid misuse and overdose deaths, including a notable increase in prescription opioid misuse between 2001 and 2013 (17), and over 42,000 opioid-related deaths in 2016 (3). Additionally, recent increases in cocaine and other stimulant use (13, 18–20) have contributed to a substantial number of hospitalizations (21, 22) and deaths (3).

Available SUD treatments typically exhibit limited success with most patients not achieving long-term abstinence (23–26). Medications for opioid use disorder (OUD) include the agonist treatments methadone and buprenorphine, and the opioid antagonist naltrexone (27). However, many people who use opioids are unable or unwilling to access these treatments or do not adhere to them consistently enough to achieve long-term improvement (28–30). There are no approved pharmacotherapies for cannabis (31) and stimulant use disorders (32), and with the exception of contingency management (33, 34), behavioral therapies generally have modest efficacy for treating SUDs (35, 36). Thus, the current public health landscape highlights an urgent need for novel, innovative strategies for treating SUDs.

Use of serotonin 2A (5-HT2A) agonist psychedelics such as lysergic acid diethylamide (LSD), psilocybin-containing mushrooms (hereafter referred to as psilocybin), peyote, and the dimethyltryptamine (DMT) containing admixture ayahuasca in both naturalistic and clinical settings have been implicated in decreased substance misuse (37–48). The strongest evidence is for LSD in the treatment of alcoholism, with six randomized studies showing an aggregated statistically significant effect for LSD improving outcomes in meta-analysis (49).

An early study in 74 male parolees with a history of chronic heroin use examined a 4- to 6-week residential treatment program involving roughly 5 weeks of preparatory therapy in conjunction with a single high-dose administration of LSD (300–450 μg), compared with treatment as usual outpatient care involving weekly group therapy (46). The LSD treatment was well tolerated among this sample, which was largely African American (76%) and with relatively low education (mean of 8.6 years). Biologically verified continuous abstinence was significantly greater in the LSD than control conditions at 6 month (32% vs. 8%) and 12 month (25% vs 5%) follow-ups (46). Epidemiological data from the 2008–2013 National Survey on Drug Use and Health showed lifetime serotonin 2A agonist psychedelic use was associated with 27% reduced risk of past year opioid dependence and 40% reduced risk of past year opioid abuse when controlling for relevant covariates (43). Preliminary observational data have shown significant reductions in cocaine use in a small sample ($n = 6$) after participation in a ceremonial ayahuasca retreat geared toward addressing substance misuse (47). Pilot clinical research currently underway has also found promising early results of psilocybin-assisted treatment in people with cocaine use disorder (50, 51). In addition to these preliminary clinical findings, anecdotal reports further corroborate potential benefits of psychedelics in people with various substance use issues (e.g., 52).

We have previously published findings on individuals who self-reported reductions in tobacco (53), and alcohol misuse (40) attributed to naturalistic psychedelic use. However, instances in which people experienced a marked reduction in problematic cannabis, opioid, or stimulant use following ingestion of a psychedelic have not been systematically documented to date. Therefore, the current study sought to characterize instances in which individuals experienced a reduction in cannabis, opioid, or stimulant use after taking a psychedelic in a non-clinical setting. We hypothesized that greater improvements in substance misuse would be associated with greater mystical-type effects of the psychedelic experience consistent with preliminary clinical data (54, 55).

MATERIALS AND METHODS

This study was conducted as a cross-sectional, anonymous (i.e., no name or IP address recorded) online survey hosted on SurveyMonkey between October 2015 and August 2017. Study advertisements were posted on social media and on websites devoted to drug discussion, education, or research such as Erowid Center (erowid.org) and the Multidisciplinary Association for Psychedelic Studies (maps.org). Ads sought individuals who had "overcome alcohol[1] or drug addiction after using psychedelics," and took interested individuals to a page detailing introductory information regarding the study aims, participation requirements (e.g., filling out a survey), and study inclusion criteria. Inclusion criteria were: (1) at least 18 years of age, (2) able to speak, read, and write English fluently, (3) self-identified as having had problematic cannabis, opioid, or stimulant use, and (4) had used a serotonin 2A agonist psychedelic[2] outside of a research or medical setting, followed by reduction or cessation of subsequent cannabis, opioid, or stimulant use. This study used purposive sampling (56) to specifically seek out people who had experienced improvements in substance use after psychedelic use for two

[1] Data on alcohol were previously published elsewhere. See (40).

[2] i.e., psilocybin [magic] mushrooms, LSD, morning glory seeds, mescaline, peyote or San Pedro cactus, DMT, or Ayahuasca.

reasons. First, to better characterize these individuals and their experiences, and second, as a preliminary step towards designing and studying psychedelic-assisted interventions for SUDs in clinical settings. People who indicated that they met inclusion criteria, understood the study procedures, and were willing to voluntarily participate were able to begin the survey. Individuals who read the introductory information and then chose to complete the survey were considered to have provided informed consent. Participants were not financially compensated for completing the survey. The study was approved by an Institutional Review Board of the Johns Hopkins University School of Medicine.

Measures

Information on participant demographics and drug use history were collected. Participants' drug use was assessed retrospectively in the periods before and after the psychedelic experience to which they attributed their reduction or cessation in drug use (hereafter referred to as "reference psychedelic experience"). This included ratings of distress related to drug use prior to the reference psychedelic experience, overall duration of drug misuse, use of medication or other SUD treatments before and after the reference psychedelic experience, age of first drug use, and lifetime presence of other mental health diagnoses.[3]

Participants provided data on the reference psychedelic experience, including the psychedelic used and approximate dose, type of setting where the experience occurred, intention for self-administering the psychedelic, and any adverse effects or other behavioral changes attributed to the reference psychedelic experience. Participants were asked about possible mechanisms of change attributed to their psychedelic-associated reductions in drug use. Participants also provided ratings of withdrawal symptom severity after the reference psychedelic experience relative to prior attempts to reduce or stop drug use. Further information on the reference psychedelic experience and related changes in drug use patterns was gathered using assessments described below. Participants were asked to identify a specific drug or class of drugs among cannabis, opioids, and stimulants, that was the primary substance of abuse that they reduced or stopped after psychedelic use, and about which they answered specifically targeted questions.

Because this survey was conducted concurrently for people reporting psychedelic-associated reductions in alcohol (40), cannabis, opioid, and stimulant use, some of the measures used here were originally designed and validated to probe alcohol use, and were adapted for this survey to assess other drug use and craving. This was done so that scores on given assessments could be meaningfully compared across drug classes, rather than compared across a number of disparate measures of consumption and/or craving. Participants completed two iterations of a modified version of the Drug Use Disorders Identification Test-Consumption (DUDIT-C), the DSM-5 Substance Use Disorder Symptom Checklist, and a modified version of the Alcohol Urge Questionnaire (AUQ), each asking specifically about the primary drug/class of interest (i.e., cannabis, opioids, or stimulants). In the first iteration, participants were asked about their drug use in the year prior to their reference psychedelic experience. In the second, they responded regarding their drug use in the time since the reference psychedelic experience.

DUDIT-C

The DUDIT is an 11-item assessment designed to screen for problematic drug use (57), which largely parallels the 10-item Alcohol Use Disorder Identification Test (AUDIT) developed by the World Health Organization to assess alcohol misuse (58). The first three items of the AUDIT probe frequency of drinking, quantity of alcohol use, and frequency of heavy use, and are often used to provide an abbreviated measure of alcohol consumption called the AUDIT-Consumption or AUDIT-C (59, 60). For this survey we administered a modified version of the DUDIT asking specifically about frequency of drug use, quantity used, and frequency of heavy use regarding the specific drug of choice identified by the participant (i.e., cannabis, opioids, or stimulants) to provide an overall score of drug consumption we identify here as DUDIT-C.

DSM-5 Substance Use Disorder Symptom Checklist

This checklist was modified to assess DSM-5 symptoms for past and current cannabis, opioid, and stimulant use disorder (4, 61). Participants endorsed whether each of the 11 diagnostic criteria for SUD were true or false based on their drug use in the year before their reference psychedelic experience, and in the time since the reference psychedelic experience. According to DSM-5 criteria, presence of 2–3 symptoms indicates a mild, four to five symptoms indicate a moderate, and six or more symptoms indicate a severe SUD (4).

Drug Urge Questionnaire (DUQ)

This instrument is a modified version of the eight-item Alcohol Urge Questionnaire (AUQ; 62). The AUQ is a validated alcohol craving measure that assesses three domains: (1) desire to drink; (2) expectation of positive effects from drinking; and (3) inability to resist drinking when alcohol is accessible, with scores ranging from 8 to 56, and higher scores indicating greater craving. For this study, items were modified to ask about craving for the specific drug of choice (i.e., cannabis, opioids, or stimulants), rather than alcohol.

Mystical Experience Questionnaire (MEQ30)

The MEQ30 is a validated 30-item questionnaire designed to assess mystical-type subjective effects of psychedelics (63–66). There are four major dimensions of the MEQ30: (1) mystical, including feelings of unity, sacredness, and noetic quality (i.e., direct knowledge or insight); (2) positive mood (e.g., awe, joy); (3) transcendence of time and space; and (4) ineffability. Participants completed the MEQ30 regarding their reference psychedelic experience. A "complete" mystical experience was defined by ≥60% of the maximum possible score on each of the four subscales of the MEQ30 (63).

[3] A copy of the survey questionnaire is available online (**Supplementary Material**).

Ratings of Persisting Effects

The personal meaning, psychological challenge, psychological insight, spiritual significance, and change in well-being or life satisfaction attributed to the reference psychedelic experience were rated by respondents (40, 67, 68). Participants rated personal meaning, psychological challenge, and psychological insight on a scale from 1 to 8 (1 = no more than routine, everyday experiences; 7 = among the five most meaningful/challenging/insightful experiences of my life; and 8 = the single most meaningful/challenging/insightful experience of my life). Spiritual significance was rated on a scale from 1 to 6 (1 = not at all; 5 = among the five most spiritually significant experiences of my life; 6 = the single most spiritually significant experience of my life). Change in well-being or life satisfaction was rated on a scale from −3 (decreased very much) to 0 (no change) to +3 (increased very much).

Data Analyses

First, descriptive statistics of background and demographic characteristics, history of psychedelic use and characteristics of psychedelic session, substance use and history of treatment, substance withdrawal symptoms, and psychiatric history were calculated. Next, all study variables were subjected to chi-square and one-way analysis of variance tests (with between-subject factor for type of substance) to examine whether there were any differences in study variables as a function of the type of substance (cannabis, opioids, stimulants) affected by the psychedelic experience.

DUDIT-C change scores (post-score minus pre-score) were examined to assess how much each participant's overall substance use had changed from pre- to post-psychedelic experience. Pearson correlation coefficients were calculated to examine the degree to which DUDIT-C change scores were associated with primary study variables (substance, age, country of residence, mean age at time of psychedelic experience, dose of psychedelic, mystical experiences, insight experiences, personal meaning of psychedelic experience, pre-DUDIT-C, substance distress prior to experience, substance craving prior to experience, post-DUDIT-C, age of first substance use). These analyses were conducted using SPSS software v.24 (69).

Finally, a path analysis was conducted to examine a model of substance use change associated with a psychedelic experience. The model included (1) Pre-DUDIT-C as a predictor of DUDIT-C change score, (2) dose of the psychedelic as a predictor of acute mystical and insight experiences during psychedelic session, (3) insight and mystical experiences as predictors of ratings of personal meaning associated with the psychedelic session, and (4) personal meaning as a predictor of DUDIT-C change score (see **Figure 1**). We also controlled for the intercorrelation of age with DUDIT-C change score and the intercorrelation of acute mystical and insightful experiences. We conducted this path analysis using maximum likelihood with robust standard errors in MPlus software v.7.0 (70).

RESULTS

Respondent Characteristics

During data collection (October, 2015 through August, 2017), 3,987 people clicked a recruitment advertisement and started filling out the survey. Of these, 2,556 met all inclusion criteria, provided informed consent, and initiated a response regarding cannabis, opioids, or stimulants. Among these, a total of 630 individuals completed the full survey regarding their use of one of these three classes of substances. Of those that completed the entire survey, 186 respondents were excluded because their reference psychedelic experience occurred within 3 months of filling out the survey, thus limiting the ability to assess lasting

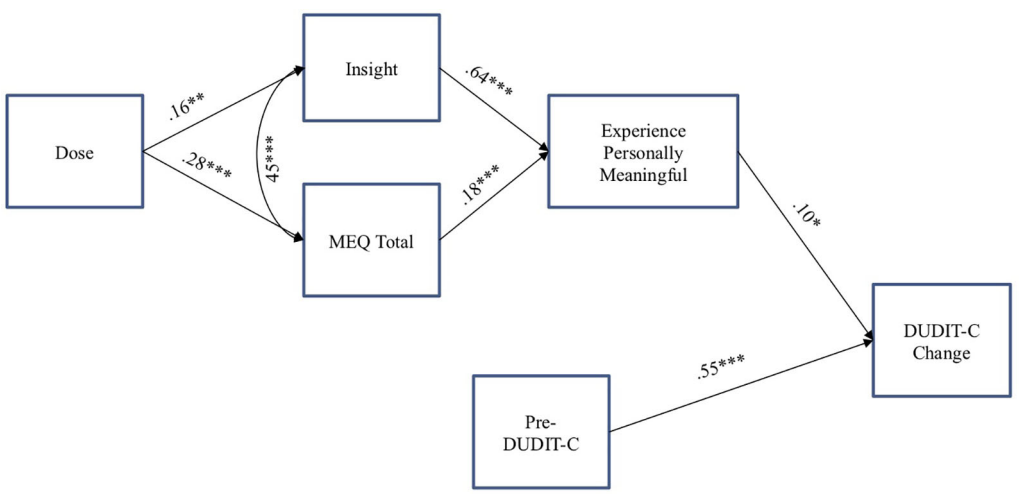

FIGURE 1 | Path analysis examining predictors of substance consumption change score from pre- to post-psychedelic experience among individuals meeting criteria for risky substance use while controlling for the positive association between acute insight and mystical experiences. *p < .05; **p < .01; ***p < .001. DUDIT-C = Drug Use Disorders Identification Test—Consumption. ME, Mystical Experience Questionnaire.

change in substance use on the modified DUDIT-C (71). The final sample was comprised of 444 adults. Demographics are presented in **Table 1**. The majority were white (82.4%), male (79.1%), and from the U.S. (66.9%), with a mean age of 28.4 (*SD* = 10.6). Of these, 166 reported they experienced a change in their cannabis use, 155 reported a change in opioid use, and 123 reported a change in stimulant use, following a psychedelic experience. It took participants a median duration of 1 h to complete the survey (inter-quartile range: 0 h 43 min to 1 h 38 min).

Substance Use, Mental Health, and Treatment History Prior to Psychedelic Experience

Table 1 shows data regarding participant history of substance use and mental health. Prior to their reference psychedelic experience, 95.7% met criteria for a SUD (severe: 78.6%, moderate: 10.6%, mild: 6.5%). Of the total sample, a minority did not meet DSM-5 criteria for SUD (4.3%) but reported prior problematic use. Mean substance use score on the retrospective DUDIT-C was 8.0 (*SD* = 2.5), suggesting respondents had a

TABLE 1 | Demographic characteristics, substance use, and mental health history in the sample (N = 444) and in each substance-specific subsample.

	Total sample (N = 444)	Cannabis (n = 166)	Opioids (n = 155)	Stimulants (n = 123)	Post-hoc
Demographics					
Age***	28.4 (10.6)	25.2 (7.8)	30.6 (11.8)	29.9 (11.0)	C < O = S
Female sex	93 (20.9%)	31 (18.7%)	35 (22.6%)	27 (22.0%)	
White	365 (82.4%)	136 (81.9%)	131 (84.5%)	98 (80.3%)	
Hispanic	38 (8.6%)	13 (7.8%)	14 (9.0%)	11 (8.9%)	
Single/not married	254 (57.2%)	105 (63.3%)	90 (58.1%)	59 (48.0%)	
United States resident***	297 (66.9%)	84 (50.6%)	123 (79.4%)	90 (73.2%)	C < O = S
Education					
Did not complete high school/GED	21 (4.7%)	11 (6.6%)	6 (3.9%)	4 (3.3%)	
High school/GED	75 (16.9%)	33 (19.9%)	18 (11.6%)	24 (19.5%)	
Some college	183 (41.2%)	61 (36.7%)	75 (48.4%)	47 (38.2%)	
College graduate	88 (19.8%)	30 (18.1%)	30 (19.4%)	28 (22.8%)	
Some grad school or graduate	77 (17.3%)	31 (18.7%)	26 (16.8%)	20 (16.3%)	
Income					
0–19.9K	137 (31.2%)	58 (35.6%)	43 (27.7%)	36 (29.8%)	
20–39.9K	106 (24.1%)	35 (21.5%)	44 (28.4%)	27 (22.3%)	
40–59.9K	64 (14.6%)	28 (17.2%)	23 (14.8%)	13 (10.7%)	
60–99.9K	67 (15.3%)	20 (12.3%)	24 (15.5%)	23 (19.0%)	
100K+	65 (14.8%)	22 (13.5%)	21 (13.5%)	22 (18.2%)	
Substance use variables and SUD diagnosis					
Substance distress***	2.6 (1.6)	1.8 (1.2)	2.9 (1.3)	3.2 (2.1)	C < O = S
Pre-DUDIT C	8.0 (2.5)	8.4 (2.1)	8.0 (2.6)	7.7 (2.7)	
Pre-DSM5					
No SUD	19 (4.3%)	9 (5.4%)	5 (3.2%)	5 (4.1%)	
Mild SUD	29 (6.5%)	11 (6.6%)	7 (4.5%)	11 (8.9%)	
Moderate SUD	47 (10.6%)	22 (13.3%)	12 (7.7%)	13 (10.6%)	
Severe SUD	349 (78.6%)	124 (74.7%)	131 (84.5%)	94 (76.4%)	
Pre-DUQ (Craving)***	40.7 (10.4)	36.6 (9.7)	45.1 (9.6)	40.7 (10.2)	C < S < O
Post-DUDIT C***	2.6 (2.8)	3.7 (2.8)	1.8 (2.5)	2.1 (2.5)	C > S = O
Post-DSM5					
No SUD	323 (72.7%)	109 (65.7%)	117 (75.5%)	97 (78.9%)	
Mild SUD	62 (14.0%)	25 (15.1%)	22 (14.2%)	15 (12.2%)	
Moderate SUD	24 (5.4%)	14 (8.4%)	3 (1.9%)	7 (5.7%)	
Severe SUD	35 (7.9%)	18 (10.8%)	13 (8.4%)	4 (3.3%)	
Post DUQ (Craving)	16.1 (8.9)	16.4 (9.0)	16.2 (9.6)	15.4 (7.8)	
Years of having a substance use problem	4.5 (5.3)	3.9 (4.8)	5.4 (5.8)	4.4 (5.2)	
Age of first use***	17.2 (4.4)	15.9 (2.3)	18.5 (5.4)	17.2 (4.7)	C < S < O
DUDIT-C Change Score***	-5.4 (3.2)	-4.7 (2.9)	-6.2 (3.4)	-5.6 (3.2)	C < O
History of mental health conditions					
Any mental health disorder	391 (88.1%)	141 (84.9%)	142 (91.6%)	108 (87.8%)	
Anxiety disorder	277 (62.4%)	102 (61.4%)	104 (67.1%)	71 (57.7%)	
Eating disorder	49 (11.0%)	21 (12.7%)	15 (9.7%)	13 (10.6%)	
Impulse control disorder	31 (7.0%)	7 (4.2%)	13 (8.4%)	11 (8.9%)	
Mood disorder	276 (62.2%)	104 (62.7%)	89 (57.4%)	83 (67.5%)	
Personality disorder	65 (14.6%)	28 (16.9%)	12 (7.7%)	25 (20.3%)	
Psychotic disorder	30 (6.8%)	8 (4.8%)	9 (5.8%)	13 (10.6%)	
Substance use disorder***	266 (59.9%)	73 (44.0%)	122 (78.7%)	71 (57.7%)	C = S < O

*All values shown are Mean (SD), except where % is noted to indicate n (%). GED, General Education Diploma; DUDIT-C, Drug Use Disorders Identification Test – Consumption; DSM5, Diagnostic and Statistical Manual of Mental Disorders; 5th Edition; SUD, Substance Use Disorder; DUQ, Drug Urge Questionnaire. ***p < .001.*

history of heavy substance use, including notable substance use-related consequences before their reference psychedelic experience (recommended AUDIT-C cutoffs for problematic use are ≥4 for men and ≥3 for women; 59). Respondents had been experiencing substance use problems for mean of 4.5 (*SD* = 5.3) years, had been using their primary substance since the mean age of 17 (*SD* = 4.4), and the mean reported distress associated with their substance use was between "a moderate amount" and "a lot" (*M* = 2.6/4, *SD* = 1.6). Mode responses regarding lifetime psychedelic use ranged from "never used" for peyote (85%), San Pedro (82%), mescaline (80%), ayahuasca (79%), morning glory seeds (70%), and DMT (pure compound; 52%), to 2–5 lifetime psilocybin uses (22%), and 11–20 lifetime LSD uses (17%). Large proportions of the sample had been diagnosed with an anxiety disorder (62%), mood disorder (62%), or a SUD not otherwise specified (60%). **Table 2** shows SUD treatment history. The majority of participants (59%) had received no treatment for their substance use prior to the reference psychedelic experience, with some having sought treatment *via* counseling (26%), self-help (17%), or support group (16%).

Reference Psychedelic Experience

Table 3 shows data regarding the reference psychedelic experience. Approximately three quarters of the sample reported using either LSD (43%) or psilocybin (29%) in the psychedelic experience that contributed to a change in substance misuse. Respondents reported using a moderate (47%), high (33%), or very high (12%) dose and most reported that at least 1 year had passed since their experience (70%), with 20% reporting 6 or more years since their experience. As **Table 3** shows, most respondents had their reference psychedelic experience in their home (59%), with the intention for psychological (61%) or spiritual (41%) exploration. Notably, only 14% reported that they intended to reduce/quit their problematic substance use through using the psychedelic substance. Although most participants did not report an explicit intention to change their substance use, 28% of respondents attributed a change in their life priorities or values to their reference psychedelic experience, which was the most commonly reported mechanism for how the psychedelic experience helped change their substance use.

Participant MEQ30 scores were 67% of maximum total score on average, with about 40% of respondents meeting criteria for a "complete mystical experience." Overall, 76% of respondents rated their reference psychedelic experience among the top 10 most personally meaningful of their lives; 45% rated it among the top 10 most psychologically challenging of their lives; and 71% rated it among the top 10 most psychologically insightful experiences of their lives. Approximately one-half of the sample (51%) rated the reference psychedelic experience among the top 5 most spiritually significant experiences of their lives, and 69% said their sense of well-being or life

TABLE 2 | Substance Use Disorder (SUD) treatment history in the sample (N = 444) and in each substance specific subsample.

	Total sample (N = 444)	Cannabis (n = 166)	Opioids (n = 155)	Stimulants (n = 123)	Post-hoc
SUD treatment history prior to psychedelic session					
None***	262 (59.0%)	122 (73.5%)	63 (40.6%)	77 (62.6%)	C = S > O
Treatment center/detox***	59 (13.3%)	7 (4.2%)	41 (26.5%)	11 (8.9%)	C = S < O
Counseling***	115 (25.9%)	24 (14.5%)	64 (41.3%)	27 (22.0%)	C = S < O
Phone counseling	13 (2.9%)	1 (.6%)	7 (4.5%)	5 (4.1%)	
Website counseling	30 (6.8%)	6 (3.6%)	17 (11.0%)	7 (5.7%)	
Hypnosis	7 (1.6%)	0 (0.0%)	7 (4.5%)	0 (0.0%)	
Acupuncture	17 (3.8%)	2 (1.2%)	11 (7.1%)	4 (3.3%)	
Support group***	72 (16.2%)	9 (5.4%)	42 (27.1%)	21 (17.1%)	C < O = S
Self-help	74 (16.7%)	17 (10.2%)	35 (22.6%)	22 (17.9%)	
Spiritual practice	61 (13.7%)	17 (10.2%)	27 (17.4%)	17 (13.8%)	
Medications (for opioid group only)					
Methadone	–	–	24 (15.5%)	–	
Naltrexone	–	–	8 (5.2%)	–	
Buprenorphine	–	–	35 (22.6%)	–	
SUD treatment history following psychedelic session					
None***	281 (63.3%)	129 (77.7%)	73 (47.1%)	79 (64.2%)	C > S > O
Treatment center/detox	16 (3.6%)	2 (1.2%)	8 (5.2%)	6 (4.9%)	
Counseling***	55 (12.4%)	9 (5.4%)	34 (21.9%)	12 (9.8%)	C = S < O
Phone counseling	4 (.9%)	0 (0.0%)	3 (1.9%)	1 (.8%)	
Website counseling	8 (1.8%)	4 (2.4%)	3 (1.9%)	1 (.8%)	
Hypnosis	4 (.9%)	0 (0.0%)	2 (1.3%)	2 (1.6%)	
Acupuncture	6 (1.4)	0 (0.0%)	4 (2.6%)	2 (1.6%)	
Support group	30 (6.8%)	5 (3.0%)	20 (12.9%)	5 (4.1%)	
Self-help***	36 (8.1%)	6 (3.6%)	25 (16.1%)	5 (4.1%)	C = S < O
Medications (for opioid group only)					
Methadone	–	–	5 (3.2%)	–	
Naltrexone	–	–	6 (3.9%)	–	
Buprenorphine	–	–	11 (7.1%)	–	
Spiritual practice	71 (16.0%)	20 (12.0%)	36 (23.2%)	15 (12.2%)	

*SUD, Substance Use Disorder. ***p < .001.*

TABLE 3 | Psychedelic experience locations, intentions, variables, beliefs, and behavioral changes in the sample (N = 444) and in each substance specific subsample.

	Total sample (N = 444)	Cannabis (n = 166)	Opioids (n = 155)	Stimulants (n = 123)	Post-hoc
Location of psychedelic experience					
Home	260 (58.6%)	98 (59.0%)	93 (60.0%)	69 (56.1%)	
Party	37 (8.3%)	20 (12.0%)	8 (5.2%)	9 (7.3%)	
Public place	30 (6.8%)	14 (8.4%)	8 (5.2%)	8 (6.5%)	
Concert	34 (7.7%)	9 (5.4%)	12 (7.7%)	13 (10.6%)	
Nature	162 (36.5%)	69 (41.6%)	48 (31.0%)	45 (36.6%)	
Religious	45 (10.1%)	19 (11.4%)	14 (9.0%)	12 (9.8%)	
Other	34 (7.7%)	8 (4.8%)	16 (10.4%)	10 (8.1%)	
Intention for psychedelic experience					
No serious intention, other people were using	14 (3.2%)	7 (4.2%)	5 (3.2%)	2 (1.6%)	
Curiosity	73 (16.4%)	33 (19.9%)	24 (15.5%)	16 (13.0%)	
Recreation	231 (52.0%)	105(63.3%)	69 (44.5%)	57 (46.3%)	
Psychological self-exploration	269 (60.6%)	97 (58.4%)	94 (60.6%)	78 (63.4%)	
Explore spirituality or the sacred	180 (40.5%)	67 (40.4%)	65 (41.9%)	48 (39.0%)	
To reduce/quit using substance***	60 (13.5%)	7 (4.2%)	32 (20.6%)	21 (17.1%)	C < O = S
Psychedelic experience variables					
Psilocybin	129 (29.1%)	51 (30.7%)	43 (27.7%)	35 (28.5%)	
LSD	192 (43.2%)	82 (49.4%)	61 (39.4%)	49 (39.8%)	
Other (e.g., DMT, mescaline)	123 (27.7%)	33 (19.9%)	51 (32.9%)	39 (31.7%)	
Psychedelic dose					
Very low	3 (.7%)	0 (0.0%)	2 (1.3%)	1 (.8%)	
Low	33 (7.4%)	22 (13.3%)	4 (2.6%)	7 (5.7%)	
Moderate	208 (46.8%)	80 (48.2%)	67 (43.2%)	61 (49.6%)	
High	146 (32.9%)	52 (31.3%)	58 (37.4%)	36 (29.3%)	
Very high	54 (12.2%)	12 (7.2%)	24 (15.5%)	18 (14.6%)	
Mean age at time of experience***	23.7 (7.8)	21.9 (6.0)	25.0 (8.7)	24.7 (8.3)	C < O = S
Time since experience					
4–6 months	72 (16.2%)	32 (19.3%)	18 (11.6%)	22 (17.9%)	
7–12 months	63 (14.2%)	32 (19.3%)	17 (11.0%)	14 (11.4%)	
1–2 years	112 (25.2%)	52 (31.3%)	34 (21.9%)	26 (21.1%)	
3–5 years	108 (24.3%)	30 (18.1%)	47 (30.3%)	31 (25.2%)	
6–10 years	50 (11.3%)	12 (7.2%)	23 (14.8%)	15 (12.2%)	
More than 10 years	39 (8.8%)	8 (4.8%)	16 (10.3%)	15 (12.2%)	
MEQ total mean (SD)***	66.8 (20.7)	63.0 (21.4)	70.8 (20.6)	66.9 (19.1)	C < O = S
MEQ complete mystical experience	178 (40.1%)	58 (34.9%)	75 (48.4%)	45 (36.6%)	
PEQ—personally meaningful	5.2 (1.4)	5.1 (1.5)	5.4 (1.4)	5.1 (1.4)	
PEQ—spiritual significance	3.2 (1.4)	3.0 (1.4)	3.3 (1.4)	3.1 (1.4)	
PEQ—challenging	3.8 (2.3)	4.1 (2.2)	3.7 (2.4)	3.4 (2.2)	
PEQ—psychological insight	5.1 (1.7)	5.1 (1.5)	5.1 (1.9)	5.0 (1.6)	
PEQ—change in well-being / life satisfaction	2.5 (1.0)	2.3 (1.3)	2.7 (0.7)	2.5 (0.9)	C < O = S
Proportion ranked each reason as most important for drug use reduction					
Increased belief in ability to quit	88 (19.8%)	26 (15.7%)	39 (25.2%)	23 (18.7%)	
Reducing stress involved with quitting	35 (7.9%)	12 (7.2%)	15 (9.7%)	8 (6.5%)	
Reframing quitting as a spiritual task	58 (13.1%)	16 (9.6%)	27 (17.4%)	15 (12.2%)	
Changing life priorities or values	126 (28.4%)	51 (30.7%)	34 (21.9%)	41 (33.3%)	
Increased delayed gratification	83 (18.7%)	39 (23.5%)	25 (16.1%)	19 (15.4%)	
Increased ability to cope with craving	40 (9.0%)	14 (8.4%)	13 (8.4%)	13 (10.6%)	
Other behavioral changes after psychedelic experience					
None	23 (5.2%)	6 (3.6%)	9 (5.8%)	8 (6.5%)	

(Continued)

TABLE 3 | Continued

	Total sample (N = 444)	Cannabis (n = 166)	Opioids (n = 155)	Stimulants (n = 123)	Post-hoc
Reduced/quit other drugs	251 (56.5%)	90 (54.2%)	98 (63.2%)	63 (51.2%)	
Started using other drugs	41 (9.2%)	14 (8.4%)	16 (10.3%)	11 (8.9%)	
Improved diet	261 (58.8%)	95 (57.2%)	98 (63.2%)	68 (55.3%)	
Worsened diet	12 (2.7%)	4 (2.4%)	4 (2.6%)	4 (3.3%)	
Increased exercise	255 (57.4%)	89 (53.6%)	93 (60.0%)	73 (59.3%)	
Decreased exercise	11 (2.5%)	8 (4.8%)	2 (1.3%)	1 (0.8%)	
Improved relationships	343 (77.3%)	123 (74.1%)	129 (83.2%)	91 (74.0%)	
Worsened relationships	25 (5.6%)	12 (7.2%)	7 (4.5%)	6 (4.9%)	
Improved career	252 (56.8%)	92 (55.4%)	91 (58.7%)	69 (56.1%)	
Worsened career	23 (5.2%)	10 (6.0%)	9 (5.8%)	4 (3.3%)	

*LSD, Lysergic acid diethylamide; DMT, N,N-Dimethyltryptamine; MEQ, Mystical Experience Questionnaire; PEQ, Persisting Effects Questionnaire. ***p < .001.*

satisfaction had increased "very much" as a result of the experience and/or contemplation of it. Two individuals (0.5%) reported strong negative change to well-being or life satisfaction attributed to the reference psychedelic experience. One of these described developing "acute HPPD, hallucinogenic perception persistence disorder [*sic*]" after taking LSD and reported ongoing reduction in cannabis use afterwards. Details regarding the other person who reported strong negative change in well-being are included in the *Adverse Effects* section below.

Adverse Effects

A majority of respondents (81%) reported no persisting adverse effects from their reference psychedelic experience; 9% reported possible adverse effects (i.e., they were unsure whether there were any adverse effects) and 10% reported definite adverse effects. Those reporting possible or definite adverse effects largely rated them as not severe or slightly severe (59% of the 19% who reported possible or definite adverse effects; e.g., transient paranoia, anxiety). Five individuals (1.1% of the total sample) reported adverse effects rated as extremely severe. Among these five individuals, two reported decreased well-being or life satisfaction related to the reference psychedelic experience (#3, moderately and #4, strongly). Four of the five extreme adverse reactions were in cannabis users, with the remaining (#1) occurring in a stimulant user.

The five extremely severe adverse effects were described as, (1) "The psychedelic experience had me convinced I am heterosexual when actually I am bisexual." (2) "Night terrors, paranoia. hallucinations; both visual and auditory, feeling like I'm leaving my body, losing my sanity. Many more; these persisted for years." (3) "Again, the bad trip gave the panic disorder and caused me massive generalized anxiety for half a decade to come. Only with abstinence from cannabis and hallucinogens, tons of medication and therapy for 6 years have I been able to come out on top from this condition of absolute existential dread triggered by the mushroom experience." (4) "After this overdose, smoking weed gave me painful and disorienting brain zaps. These reduced in severity over approximately 2 weeks and changed into anxiety…. I'm not sure why I even kept smoking, it was a terrible experience but I think I was depressed from the overall after affects and still needed some sort of escape (weed had always been my favorite escape)." (5) "Had nightmares for 6 months and lived in constant fear of death, experienced tactile hallucinations and heard voices for months. Took a long time to process the shame that came through this experience. It's all been beautifully necessary, however."

Among these individuals reporting extreme adverse reactions, one reported prior history of depression and obsessive-compulsive disorder, one reported history of anxiety, mood, personality, and oppositional defiant disorders, one reported a history of anxiety and attention deficit hyperactivity disorders, one reported a history of anxiety, mood, eating, and personality disorders, and one reported a history of anxiety, mood, personality, and psychotic disorders. Thus, all these individuals reported some mental health conditions that may have been related to or contributed to adverse effects. However, because the survey did not probe whether these issues developed before or after the reference psychedelic experience, no causal attributions can be inferred from the present data.

Substance-Specific Differences in Demographics and Other Variables

As shown in **Tables 1–3**, few differences were found between cannabis, opioid, and stimulant using groups on demographic variables, substance use and treatment history, and psychedelic-related variables. When differences were found it was frequently the cannabis-using group that was different from the other substance use groups. For example, cannabis users were significantly younger and fewer of them were from the United States, compared to opioid and stimulant users. Additionally, cannabis users had lower mean ratings of substance-related distress, substance craving prior to the reference psychedelic experience, age of first primary substance use, and DUDIT-C change scores compared to opioid and stimulant users. When examining the proportion of respondents who received SUD treatment prior to and following the psychedelic experience, smaller proportions of cannabis and stimulant users had sought treatment including detoxification and counseling, compared to opioid users, but a larger proportion of them had engaged in self-help prior to the psychedelic experience. Furthermore, a larger proportion of opioid users sought treatment following the reference psychedelic experience, and more of them had been previously diagnosed with a substance use disorder, compared to cannabis or stimulant users. Cannabis users also had significantly lower MEQ30 total scores, and ratings of change in well-being or life satisfaction, than opioid users.

TABLE 4 | Withdrawal severity after psychedelic-associated cannabis cessation or reduction in comparison with previous quit attempts. (n = 166).

Withdrawal Symptom	n[a]	Symptom Severity				
		Much less severe n (%)	Less severe n (%)	Same n (%)	More severe n (%)	Much more severe n (%)
Lack of appetite	75	18 (24.0%)	13 (17.3%)	**31 (41.3%)**	12 (16.0%)	1 (1.3%)
Fatigue	87	24 (27.6%)	20 (23.0%)	**30 (34.5%)**	7 (8.0%)	6 (6.9%)
Headaches	70	19 (27.1%)	15 (21.4%)	**25 (35.7%)**	11 (15.7%)	0 (.0%)
Drowsiness	72	19 (26.4%)	16 (22.2%)	**24 (33.3%)**	11 (15.3%)	2 (2.8%)
Fever	24	4 (16.7%)	2 (8.3%)	**17 (70.8%)**	0 (.0%)	1 (4.2%)
Nausea	34	8 (23.5%)	6 (17.6%)	**17 (50.0%)**	3 (1.8%)	0 (.0%)
Tremors	41	11 (26.8%)	6 (14.6%)	**16 (39.0%)**	6 (14.6%)	2 (4.9%)
Increased heart rate	45	11 (24.4%)	10 (22.2%)	**16 (35.6%)**	4 (8.9%)	4 (8.9%)
Chills	35	9 (25.7%)	4 (11.4%)	**16 (45.7%)**	5 (14.3%)	1 (2.9%)
Seizures	18	3 (16.7%)	1 (5.6%)	**14 (77.8%)**	0 (.0%)	0 (.0%)
Hallucinations	30	4 (13.3.%)	3 (10.0%)	**13 (43.3%)**	7 (23.3%)	3 (10.0%)
Cravings	110	**62 (56.4%)**	20 (18.2%)	17 (15.5%)	6 (5.5%)	5 (4.5%)
Depression	113	**45 (39.8%)**	23 (20.4%)	20 (17.7%)	15 (13.3%)	10 (8.8%)
Confusion	70	**23 (32.9%)**	13 (18.6%)	17 (24.3%)	9 (12.9%)	8 (11.4%)
Heart pounding	49	**17 (34.7%)**	4 (8.2%)	16 (32.7%)	7 (14.3%)	5 (10.2%)
Difficulty concentrating	100	**32 (32.0%)**	25 (25.0%)	22 (22.0%)	10 (10.0%)	11 (11.0%)
Irritability	94	**30 (31.9%)**	27 (28.7%)	17 (18.1%)	15 (18.1%)	5 (5.3%)
Insomnia	110	**32 (29.1%)**	17 (15.5%)	26 (23.6%)	21 (19.1%)	14 (12.7%)
Restlessness	95	**27 (28.4%)**	22 (23.2%)	23 (24.2%)	17 (17.9%)	6 (6.3%)
Anxiety	100	**28 (28.0%)**	27 (27.0%)	20 (20.0%)	12 (12.0%)	13 (13.0%)

[a]*Sample size varies by symptom (range = 18–113), as some participants had never experienced particular withdrawal symptoms. Percentages were calculated based on the number of individuals who reported a particular withdrawal symptom.*

Modal responses shown in bold type.

Substance-Specific Withdrawal Symptoms

Table 4 shows several withdrawal symptoms were endorsed by roughly two-thirds of the cannabis-using subsample, including depression (68%), craving (66%), and insomnia (66%). Despite experiencing these withdrawal symptoms, many of these respondents (range = 45%–75%) reported that these symptoms were "less severe" or "much less severe" after the reference psychedelic experience compared to prior quit attempts. Although less frequently reported, many respondents endorsed experiencing anxiety (60%), difficulty concentrating (60%), restlessness (57%), irritability (57%), and fatigue (52%). Most reported that the symptom severity was the same or less/much less severe compared to prior quit attempts. Of particular interest, craving appeared to be dampened in those who had previously experienced this withdrawal symptom, with 56% reporting that their cannabis craving was much less severe after the reference psychedelic experience compared to prior quit attempts.

Table 5 shows approximately three quarters of the opioid-using subsample reported the following withdrawal symptoms after the reference psychedelic experience: depression (77%), irritability (76%), craving (75%), fatigue (74%), muscle aches (72%), insomnia (72%), restlessness (72%), anxiety (71%), and difficulty concentrating (70%). Despite experiencing these withdrawal symptoms, large proportions (range = 49%–75%) rated these symptoms as "less severe" or "much less severe" after the reference psychedelic experience compared to prior quit attempts. Similar to cannabis-using respondents, craving seemed to be attenuated among opioid users who had previously experienced this withdrawal symptom, with 75% reporting that their opioid craving was less or much less severe after the reference psychedelic experience compared to prior quit attempts.

Table 6 shows more than three quarters of the stimulant-using sample reported the following withdrawal symptoms after the reference psychedelic experience: depression (84%), irritability (79%), craving (77%), anxiety (77%), and difficulty concentrating (76%). Despite experiencing these withdrawal symptoms, large proportions (range = 53%–65%) reported that these symptoms were "less severe" or "much less severe" after the reference psychedelic experience compared to prior quit attempts. Similar to cannabis- and opioid-using respondents, craving seemed to be attenuated among stimulant users who had previously experienced this withdrawal symptom, with 65% reporting that their stimulant craving was less or much less severe compared to prior quit attempts.

Substance Consumption Following the Psychedelic Experience

Over 70% of participants (n = 331) reported that they had greatly reduced or quit using their primary substance following their reference psychedelic experience as evidenced by an average DUDIT-C change score of −5.4 (SD = 3.2; range = 4 to −12). Though 95.7% met SUD criteria before the reference psychedelic experience, only 27.3% met criteria for a SUD in the time since their reference psychedelic experience. Small proportions continued to meet criteria for mild (14%), moderate (5%), and severe (8%) SUDs. Overall, the average post-DUDIT-C score (M = 2.6; SD = 2.8) suggested that most respondents were no

TABLE 5 | Withdrawal severity after psychedelic-associated opioid cessation or reduction in comparison with previous quit attempts. (n = 155).

Withdrawal Symptom	n[a]	Symptom Severity				
		Much less severe n (%)	Less severe n (%)	Same n (%)	More severe n (%)	Much more severe n (%)
Lacrimation	92	26 (28.3%)	17 (18.5%)	**39 (42.4%)**	7 (7.6%)	3 (3.3%)
Rhinorrhea	93	24 (25.8%)	20 (21.5%)	**39 (41.9%)**	7 (7.5%)	3 (3.2%)
Fever	72	25 (34.7%)	11 (15.3%)	**28 (38.9%)**	6 (8.3%)	2 (2.8%)
Muscle aches	112	34 (30.4%)	21 (18.8%)	**43 (38.4%)**	7 (6.3%)	7 (6.3%)
Diarrhea	94	32 (34.0%)	17 (18.1%)	**36 (38.3%)**	4 (4.3%)	5 (5.3%)
Headaches	100	32 (32.0%)	19 (19.0%)	**37 (37.0%)**	6 (6.0%)	6 (6.0%)
Heart pounding	100	26 (26.0%)	21 (21.0%)	**37 (37.0%)**	8 (8.0%)	8 (8.0%)
Drowsiness	106	24 (22.6%)	24 (22.6%)	**39 (36.8%)**	10 (9.4%)	9 (8.5%)
Chills	107	35 (32.7%)	24 (22.4%)	**37 (34.6%)**	4 (3.7%)	7 (6.5%)
Insomnia	111	34 (30.6%)	21 (18.9%)	**37 (33.3%)**	7 (6.3%)	12 (10.8%)
Increased heart rate	100	30 (30.0%)	23 (23.0%)	**33 (33.0%)**	9 (9.0%)	5 (5.0%)
Restlessness	111	30 (27.0%)	**33 (29.7%)**	33 (29.7%)	6 (5.4%)	9 (8.1%)
Fatigue	115	32 (27.8%)	**33 (28.7%)**	33 (28.7%)	9 (7.8%)	8 (7.0%)
Cravings	116	**58 (50.0%)**	29 (25.0%)	15 (12.9%)	6 (5.2%)	8 (6.9%)
Irritability	118	**53 (44.9%)**	21 (17.8%)	28 (23.7%)	8 (6.8%)	8 (6.8%)
Depression	120	**53 (44.2%)**	31 (25.8%)	19 (15.8%)	9 (7.5%)	8 (6.7%)
Anxiety	110	**44 (40.0%)**	26 (23.6%)	24 (21.8%)	8 (7.3%)	8 (7.3%)
Seizures	33	**13 (39.4%)**	4 (12.1%)	12 (36.4%)	1 (3.0%)	3 (9.1%)
Nausea	98	**34 (34.7%)**	25 (25.5%)	29 (29.6%)	4 (4.1%)	6 (6.1%)
Tremors	90	**31 (34.4%)**	19 (21.1%)	27 (30.0%)	10 (11.1%)	3 (3.3%)
Lack of appetite	107	**34 (31.8%)**	25 (23.4%)	32 (29.9%)	10 (9.3%)	6 (5.6%)
Difficulty concentrating	109	**33 (30.3%)**	24 (22.0%)	33 (30.3%)	10 (9.2%)	9 (8.3%)

[a]*Sample size varies by symptom (range = 33–120), as some participants had never experienced particular withdrawal symptoms. Percentages were calculated based on the number of individuals who reported a particular withdrawal symptom.*
Modal responses shown in bold type.

TABLE 6 | Withdrawal severity after psychedelic-associated stimulant cessation or reduction in comparison with previous quit attempts. (n = 123).

Withdrawal Symptom	n[a]	Symptom Severity				
		Much less severe n (%)	Less severe n (%)	Same n (%)	More severe n (%)	Much more severe n (%)
Fever	46	8 (17.4%)	9 (19.6%)	**26 (56.5%)**	1 (2.2%)	2 (4.3%)
Heart pounding	73	16 (21.9%)	21 (28.8%)	**29 (39.7%)**	4 (5.5%)	3 (4.1%)
Psychomotor retardation	75	20 (26.7%)	23 (30.7%)	**27 (36.0%)**	4 (5.3%)	1 (1.3%)
Increased appetite	87	15 (17.2%)	19 (21.8%)	**31 (35.6%)**	17 (19.5%)	5 (5.7%)
Drowsiness	87	17 (19.5%)	23 (26.4%)	**30 (34.5%)**	12 (13.8%)	5 (5.7%)
Unpleasant dreams	70	13 (18.6%)	22 (31.4.%)	**23 (32.9%)**	7 (10.0%)	5 (7.1%)
Increased heart rate	77	18 (23.4%)	24 (23.4%)	**25 (32.5%)**	8 (10.4%)	2 (2.6%)
Psychomotor agitation	69	19 (27.5%)	18 (26.1%)	**21 (30.4%)**	8 (11.6%)	3 (4.3%)
Difficulty concentrating	93	24 (25.8%)	25 (26.9%)	**28 (30.1%)**	10 (10.8%)	6 (6.5%)
Headaches	83	20 (24.1%)	22 (26.5%)	**24 (28.9%)**	11 (13.3%)	6 (7.2%)
Restlessness	89	19 (21.3%)	**31 (34.8%)**	20 (22.5%)	14 (15.7%)	5 (5.6%)
Confusion	68	16 (23.5%)	**23 (33.8%)**	22 (32.4%)	7 (10.3%)	0 (.0%)
Irritability	97	27 (27.8%)	**31 (32.0%)**	18 (18.6%)	15 (15.5%)	6 (6.2%)
Fatigue	88	20 (22.7%)	**26 (29.5%)**	26 (29.5%)	12 (13.6%)	4 (4.5%)
Insomnia	87	17 (19.5%)	**24 (27.6%)**	24 (27.6%)	13 (14.9%)	9 (10.3%)
Cravings	95	**40 (42.1%)**	22 (23.2%)	18 (18.9%)	8 (8.4%)	7 (7.4%)
Anxiety	95	**33 (34.7%)**	30 (31.6%)	16 (16.8%)	11 (11.6%)	5 (5.3%)
Depression	103	**35 (34.0%)**	29 (28.2%)	17 (16.5%)	13 (12.6%)	9 (8.7%)

[a]*Sample size varies by symptom (range = 46–103), as some participants had never experienced particular withdrawal symptoms. Percentages were calculated based on the number of individuals who reported a particular withdrawal symptom.*
Modal responses shown in bold type.

longer using substances above the threshold for which he/she would be considered a risky substance user based on established cutoffs for the AUDIT-C (≥4 for males, ≥3 for females; 59). Additionally, most participants (63%) did not seek other treatment for substance use after their reference psychedelic experience, but smaller proportions noted they engaged in a spiritual practice (16%), had received counseling (12%), or attended a support group (7%).

TABLE 7 | Correlation among study variables.

		1	2	3	4	5	6	7	8	9	10	11	12	13
1	DUDIT-C change score		**0.19**	−0.07	**0.19**	**0.42**	**0.56**	**−0.67**	−0.01	**0.19**	0.12	**0.18**	**0.17**	0.09
2	Age			−0.06	0.00	0.03	0.11	−0.13	**0.36**	**0.74**	0.00	−0.07	0.00	0.03
3	Country				−0.03	−0.13	0.00	0.09	0.03	−0.02	−0.13	−0.02	−0.07	0.02
4	Substance distress					**0.30**	0.06	**−0.17**	0.15	0.05	0.09	0.15	0.07	0.05
5	Pre-DUQ Craving						**0.50**	−0.05	−0.04	0.04	**0.26**	**0.26**	**0.31**	0.16
6	Pre DUDIT-C							**0.24**	−0.10	0.14	0.09	0.12	0.14	0.11
7	Post DUDIT-C								−0.08	−0.10	−0.06	−0.10	−0.08	−0.01
8	Age of first use									**0.42**	−0.12	−0.06	−0.04	−0.03
9	Mean age at time of experience										0.04	−0.03	0.02	−0.01
10	MEQ Mean											**0.48**	**0.49**	**0.28**
11	Insight												**0.73**	**0.17**
12	Meaning													**0.18**
13	Dose													

Bolded values are significant correlations at p < .001 (conservative alpha). DUDIT-C, Drug Use Disorders Identification Test – Consumption; DUQ, Drug Urge Questionnaire; MEQ, Mystical Experience Questionnaire.

Path Analysis

Table 7 shows Pearson correlations among variables. As shown in the table, greater decreases in consumption as quantified by DUDIT-C change scores were significantly associated with greater age, ratings of the experience as personally meaningful and insightful, pre-DUDIT-C scores, and intensity of substance use distress. Aside from significant correlations with DUDIT-C change scores, clusters of variables within the overall matrix that were significantly positively correlated included mystical and persisting effects of the reference psychedelic experience (e.g., greater MEQ30 scores associated with greater meaning and insight), and substance use variables (e.g., greater pre-DUQ craving associated with greater substance-related distress).

Based on previously published survey data among individuals reporting reductions in alcohol consumption after taking a serotonin 2A agonist psychedelic (40), and informed by the present correlation data on variables associated with change in DUDIT-C substance use scores, a path analysis was conducted examining a proposed model to explain the effect of psychedelic consumption on problematic substance use reduction (**Figure 1**). While controlling for the positive association between acute insight and mystical experiences, greater substance consumption prior to the reference psychedelic experience (pre-DUDIT-C) was directly related to greater change in substance use (DUDIT-C change score). Higher doses of the psychedelic substance were directly related to higher intensity of acute mystical and insight experiences during the psychedelic session, both of which were directly related to greater personal meaning of the experience. Moreover, higher ratings of personal meaning were directly related to greater DUDIT-C change score. Two indirect effects were also found between greater intensity of acute mystical effects [β = .02, SE = .01, p < .05, 95% CI (.00,.03)] and insight [β = .07, SE = .03, p < .05, 95% CI (.01,.11)] on higher DUDIT-C change score *via* higher ratings of personal meaning. Model fit was good, X^2 (7, N = 444) = 10.13, p = .181; root-mean-square error of approximation = .03 [CI (.00,.07)], standardized root-mean-square residual = .040, and Tucker-Lewis index = .99.

DISCUSSION

The current study provides data on 444 individuals who self-reported reductions in cannabis, opioid, and stimulant misuse after taking a psychedelic drug in a non-clinical setting. The majority of respondents retrospectively reported meeting DSM-5 criteria for severe SUD before their psychedelic experience, whereas in the time since that experience, the majority no longer met criteria for any SUD. Most of the respondents claimed lasting reductions in their substance use for over 1 year after using a psychedelic, consistent with persisting benefits observed in laboratory studies with psilocybin (54, 55, 72–74). Serious adverse effects, though relatively rare, were reported and included both ongoing perceptual disturbances described as hallucinogen persisting perception disorder (HPPD; 75), and persisting psychotic symptoms such as paranoia and hallucinations. These were more common among individuals reporting reductions in cannabis use after the reference psychedelic experience, possibly related to observed associations between cannabis use and psychosis (76). Despite adverse events being rare, these data highlight the potential risks of psychedelic use in naturalistic settings by individuals who have not received medical screening or preparation, as is common practice in clinical trials involving psychedelic administration (77). A minority of the present sample (range = 2.5–9.2%) reported negative impacts on overall life adjustment, including increased use of other drugs (**Table 3**), indicating some cases in which outcomes may have been mixed or otherwise undesirable. Such cases warrant further study to examine what factors may be associated with these challenges.

The findings of the present study are limited by the nature of the anonymous, retrospective self-report data collected, which cannot be verified, and are subject to participant self-selection and recall bias. The cross-sectional design does not allow for causal inferences to be derived from the findings, nor is this study able to provide any information regarding the overall prevalence of psychedelic-associated reductions in other substance use. The purposive sampling used in the current study specifically sought out people reporting positive outcomes regarding substance misuse after

naturalistic psychedelic use to characterize these cases, therefore data were not explicitly collected on instances where psychedelic use led to no change or exacerbation of drug misuse. This method limits our ability to generalize these findings across all psychedelic users with other substance misuse issues (e.g., 78, 79), but provides valuable information for designing future psychedelic-assisted treatments for SUD. Additionally, because the survey sought to assess changes in drug use across several pharmacological classes, modified versions of alcohol assessments (AUDIT-C and AUQ) were used, which have not been validated for use in this manner. Due to these limitations, the current data should be interpreted with caution. However, taken in combination with preliminary clinical findings (46, 49, 54, 80) and previous anonymous survey studies (40, 55), these results further bolster the potential utility of serotonergic psychedelics as aids in the treatment of addiction.

Congruent with findings from prior surveys on individuals reporting reductions in tobacco (55) and alcohol consumption (40) after naturalistic psychedelic use, the current sample reported cravings for their primary problematic substance to be less or much less severe than previous attempts to reduce or stop using (**Tables 4–6**). While the veracity and underpinnings of such psychedelic-associated craving reductions remain uncertain, that these patterns of responses are stable across several unrelated drug classes is noteworthy and points to a potential mechanism by which psychedelics may help reduce subsequent substance misuse. Although lifetime psychedelic use was queried, we did not collect the information necessary to make any chronological inference regarding whether reference psychedelic experiences that were closer to initial psychedelic use were more or less likely to impact other substance misuse, a question that remains for future research.

Participants also reported less severity of anxiety and depression symptoms after the reference psychedelic experience compared with other attempts to reduce their substance use. A growing body of literature has shown persisting anxiolytic effects of psilocybin (81–83) and LSD (84), and antidepressant effects of psychedelics including psilocybin (85–87) and ayahuasca (88). Furthermore, data suggest ayahuasca's antidepressant effects are associated with post-acute modulation of cortisol (89) and brain-derived neurotrophic factor (BDNF; 90), shedding light on possible biological mechanisms of psychedelics' lasting mood effects. In turn, reductions in anxiety and depressed mood may also help individuals remain abstinent from drugs in the post-acute "after-glow" period by improving their outlook and ability to manage withdrawal (91, 92).

Additionally, participants endorsed changes in life priorities or values, increased belief in their ability to abstain, and increased ability to delay gratification, as among the most important reasons their psychedelic experience impacted other substance use. These data are in agreement with prior surveys of people reporting psychedelic-associated reductions in tobacco (55) and alcohol consumption (40), and are in accordance with hypotheses regarding psychedelic-related changes in values, self-efficacy, and decision-making as relevant psychological mechanisms for addiction treatment (93–96). As in prior surveys on psychedelic-associated reductions in alcohol consumption (40) participants reported high levels of personal meaning, psychological insight, and mystical-type effects, which were associated with higher psychedelic dose and greater reported change in drug consumption after the psychedelic experience. Thus, the psychological impact of these experiences and acute subjective drug effects seem to play an important role in facilitating subsequent change in substance misuse as observed in pilot studies of psilocybin-assisted interventions for tobacco (55, 97) and alcohol dependence (54).

Preclinical data are further elucidating our understanding of psychedelics' biological mechanisms, with recent findings showing serotonergic psychedelics can promote structural and functional neural plasticity (98), and have potent anti-inflammatory effects (99), which may be correlated with observed therapeutic benefits. Animal models suggest diverse anti-addictive properties of serotonergic psychedelics for alcohol (100, 101) as well as other drugs of abuse. Ayahuasca has been shown to reduce amphetamine self-administration in adolescent rats and normalize amphetamine related locomotor behavior (102). Vargas-Perez and colleagues found a single administration of the serotonin 2A agonist psychedelic 4-AcO-DMT (103) prevented development of opioid and nicotine dependence and blunted withdrawal response in rats and mice (104). Together, these data suggest serotonin 2A psychedelics may hold considerable potential as novel therapeutics in treating various SUDs.

Although medications for opioid use disorder exist, the present opioid overdose rates indicate the need for different treatment avenues (3, 29, 30). For cannabis (31) and stimulant (32) use disorders there are no approved medications at present and limited treatment options, underscoring the necessity for new treatments and approaches. Psychedelic-assisted interventions for addictions may offer an attractive alternative to current treatment models in that they may result in lasting change in substance misuse after only one or a few psychedelic administration sessions (e.g., 55). Importantly, serotonin 2A psychedelics are not themselves physiologically addictive (105), yet they seemingly enhance processes often targeted by accepted addiction treatments such as insight, self-efficacy, and spirituality, which may underlie these lasting effects (93, 94, 96). While challenges remain for the development of psychedelics as medications (106, 107), converging evidence reveals a compelling signal of efficacy. Given the current public health landscape and state of addiction treatment (1, 3), this potential demands rigorous clinical research efforts and federal funding. Although psychedelics might not be a "magic bullet" to solve the pervasive issues of substance misuse and addiction, they may well constitute a much-needed addition to our current armamentarium of medication-assisted treatment for SUDs.

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available. Data may be made available on a case by case basis at the discretion of the Principal Investigator.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Johns Hopkins University School of Medicine Institutional Review Board. Written informed consent to participate in this study was not required as per local legislation and national guidelines.

AUTHOR CONTRIBUTIONS

AG-R made substantial contributions to the conception and design of the study, the acquisition and interpretation of the data, and the drafting of the manuscript. AD made substantial contributions to the conception and design of the study, the analysis and interpretation of the data, and the drafting of the manuscript. EE made substantial contributions to the design of the study, participant recruitment, and made critical revisions to the manuscript. FE made substantial contributions to the design of the study, participant recruitment, and made critical revisions to the manuscript. RG made substantial contributions to the conception and design of the study and made critical revisions to the manuscript. MJ made substantial contributions to the conception and design of the study, the acquisition and interpretation of the data, and made critical revisions to the manuscript. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00955/full#supplementary-material

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Population Survey Data Informing the Therapeutic Potential of Classic and Novel Phenethylamine, Tryptamine, and Lysergamide Psychedelics

James D. Sexton[1], *Charles D. Nichols*[2] *and Peter S. Hendricks*[1]*

[1] Department of Health Behavior, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States, [2] Department of Pharmacology and Experimental Therapeutics, LSU Health Sciences Center, New Orleans, LA, United States

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***Correspondence:**
Peter S. Hendricks
phendricks@uab.edu

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Introduction: The majority of contemporary psychedelic research has focused on ayahuasca, lysergic acid diethylamide, and psilocybin, though there are hundreds of novel psychedelic compounds that may have clinical utility. The purpose of the present study was to evaluate the therapeutic potential of classic and novel phenethylamine, tryptamine, and lysergamide psychedelics *via* a large, nationally representative population-based survey.

Methods: We tested the unique associations of lifetime classic and novel phenethylamine, tryptamine, and lysergamide psychedelics with past month psychological distress and past year suicidality among respondents pooled from years 2008–2017 of the National Survey on Drug Use and Health (weighted N = 260,964,827).

Results: Lifetime classic tryptamine use was associated with a decreased odds of past month psychological distress [aOR = 0.76; (0.69–0.83)] and past year suicidal thinking [aOR = 0.79; (0.72–0.87)]. Lifetime novel phenethylamine use, on the other hand, was associated with an increased odds of past year suicidal thinking [aOR = 1.44; (1.06–1.95)] and past year suicidal planning [aOR = 1.60; (1.06–2.41)]. No other significant associations were found.

Discussion and Conclusions: These findings, which may be driven by differences in pharmacodynamics, suggest that classic tryptamines may hold the greatest therapeutic potential of the psychedelics, whereas novel phenethylamines may pose risk for harm. The present findings thus support continued research on the clinical application of classic tryptamines. Though the current results caution against the clinical utility of novel phenethylamines, further study of these and other novel psychedelic substances is nonetheless warranted to better understand their potential application.

Keywords: phenethylamines, tryptamines, lysergamides, psychedelic-assisted therapy, mental health outcomes

INTRODUCTION

Classic psychedelics, which include dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), mescaline, and psilocybin, have been studied clinically, anthropologically, and sociologically (1, 2). Classic psychedelics appear to be both generally safe and potentially therapeutic in the treatment of anxiety disorders, mood disorders, and substance use disorders (3–7). Consistent with findings from clinical trials, population-level analyses demonstrate that lifetime classic psychedelic use is associated with a reduced likelihood of past month psychological distress and past year suicidality (8). Lifetime psilocybin use in particular evinced these protective associations above and beyond other lifetime classic psychedelic use in one analysis, suggesting that psilocybin may have unique therapeutic potential (9), however, this analysis collapsed all non-psilocybin classic psychedelics across the three primary categories of classic psychedelics: phenethylamines (mescaline and the mescaline-containing cacti peyote and San Pedro), tryptamines (DMT and the DMT-containing admixture ayahuasca; psilocybin is also a tryptamine), and lysergamides (LSD). Whether the unique protective associations of psilocybin apply to all tryptamines, and whether tryptamines in general may have unique therapeutic potential relative to phenethylamines and lysergamides is unknown.

Novel psychedelics, which also comprise phenethylamines, tryptamines, and lysergamides, are distinct from classic psychedelics in that they lack both the long history of human use and substantial research data investigating their general safety, though there are notable pharmacologic and chemical data on these substances (10–13). From 2005 to 2017, novel phenethylamines (i.e. 2,5-Dimethoxy-4-"X"-phenethylamine or 2C-X, N-Benzyl Derivatives or NBOME's) accounted for the majority of novel drug mentions in the National Survey on Drug Use and Health (NSDUH) (14), suggesting naturalistic use of these substances is on the rise. One population-level analysis found that lifetime novel psychedelic use is rare, accounted for primarily by phenethylamines, and associated with an increased likelihood of past month psychological distress and past year suicidality relative to lifetime use of classic psychedelics only (15). This suggests that novel psychedelics may be distinct from and carry reduced therapeutic potential relative to classic psychedelics. However, as with the abovementioned analysis, this analysis collapsed all classic psychedelics across phenethylamines, tryptamines, and lysergamides, and collapsed all novel psychedelics across a variety of subcategories, potentially obscuring any meaningful differences between the three primary categories of novel psychedelics. Whether each of the three categories of novel psychedelics may be distinct from and carry reduced therapeutic potential relative to each of the three categories of classic psychedelics is unknown.

Exploring the therapeutic potential of classic and novel phenethylamine, tryptamine, and lysergamide psychedelics is relevant considering that psychedelic research is experiencing a modest but growing resurgence. Whereas almost all contemporary research is accounted for by ayahuasca, LSD, and psilocybin (16), there are hundreds of novel psychedelic compounds that might have clinical utility (17, 18), with population-based survey respondents reporting the use of over 40 such compounds (15). Winnowing down this extensive list of psychedelic substances to those most likely to carry therapeutic benefit would help direct future study. Though classic and novel phenethylamine, tryptamine, and lysergamide psychedelics share important similarities (e.g. 5-HT2A receptor agonism), they differ in chemical structure, which appears to account for differences in reported subjective effects (19). It is known that psychedelics interact differently with their target 5-HT_{2A} receptor (20). That is to say, they engage with different sets of amino acid residues in the binding pocket of the receptor to produce slightly different active state conformations of the receptor. The differences in conformational states lead to known differential or biased recruitment of second messenger and effector pathways that ultimately alter the physiology of the cell or neuron such that how the classic lysergamide psychedelic LSD alters cellular physiology is slightly different from how the classic phenethylamine psychedelic mescaline does. Indeed, it is has been hypothesized that these functional differences in receptor/ligand interactions and differential effects on cellular physiology are linked to their respective subjective experiences (21).

The purpose of this study was to test for unique associations of lifetime use of classic and novel phenethylamines, tryptamines, and lysergamide psychedelics with mental health outcomes using data from a large, nationally representative population-based survey. Considering the regulatory and other complexities associated with administering psychedelic substances to humans, population-based surveys represent useful springboards for exploring the therapeutic potential of these compounds (8). Thus, the present analysis will provide preliminary evidence with regard to which categories of classic and novel psychedelics might hold the greatest therapeutic potential, thereby informing future clinical research.

METHODS

Data

Data were obtained from the publicly available NSDUH, a survey of the general, non-institutionalized United States population aged 12 and older administered by the Substance Abuse and Mental Health Services Administration of the US Department of Health and Human Services. The survey uses a multistage probability sampling design where individuals are randomly selected within a roster that accounts for state population size and housing inventory. NSDUH interviewers met with respondents in their homes, who listened to pre-recorded interview guides on headphones and responded via computer prompt. We combined the data from 2008–2017 in order to maximize sample size while maintaining standardized assessment procedures introduced in 2008. The comprehensive NSDUH sampling and questionnaire methodology can be found on their website https://nsduhweb.rti.org/respweb/about_nsduh.html.

Respondents

Using SPSS syntax, individual respondents from the 2008–2017 NSDUH were given a unique identifier and combined into a single database using the Cantor pairing function for a total unweighted sample of 562,072 cases. The analytic sample included all respondents with valid responses to the primary and

secondary variables, yielding a total unweighted sample size of 354,535 (see **Supplementary Table 1** for psychosocial characteristics of the sample). The *Analysis* section includes sample sizes for each regression model as the sample sizes varied based upon the dependent variable used. Respondents reporting mescaline (MESC2 = 1 and code 603 from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1), peyote or San Pedro (cacti that contains mescaline; PEYOTE2 = 1 and code 602 and 6077 respectively from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1), were coded as positive for lifetime classic phenethylamine use. Respondents reporting they had ever, even once used DMT (code 616 from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1), ayahuasca (an admixture that contains DMT; code 6103 from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1), or psilocybin (PSILCY2 = 1 and code 604 from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1) were coded as positive for lifetime classic tryptamine use. Respondents who reported using LSD (LSDFLAG = 1, and code 601 from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1) were coded positive for lifetime classic lysergamide use, whereas those reporting they had never used any of the aforementioned substances were coded as negative for each respective drug category (8, 9, 15). Respondents were given the option to write-in other "hallucinogens" they had used, and novel psychedelics were gathered from write-in responses as per Sexton et al. (15). **Table 1** lists both classic and novel psychedelic compounds and their classification for the purposes of this analysis. Respondents who indicated they had ever taken a substance that was classified as a novel phenethylamine (code in **Table 1** from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1) were coded as positive for lifetime novel phenethylamine use. Respondents who indicated they had ever taken a substance that was classified as a novel tryptamine (code in **Table 1** from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1) were coded as positive for lifetime novel tryptamine use. Respondents who indicated they had ever taken a substance that

TABLE 1 | Psychedelic compounds reported by respondents from the 2008–2017 National Survey on Drug Use and Health (NSDUH), respective NSDUH codes, and citations to supporting literature.

Classic Phenethylamines

Peyote (code 602; variable PEYOTE2)

San Pedro (code 6077)

Mescaline (code 603; variable MESC)

Novel Phenethylamines

2C-B (code 698) (29)
2C-C (code 6197, 6139) (31)
2C-D (code 6154) (31)
2C-E (code 6138) (31)
2C-I (code 6126) (31)
2C-P (code 6182) (29)
2C-T-2 (code 6112) (31)
2C-T-7 (code 6100) (29)
2C-T-21(code 6172) (35)
2C-x (code 6143) (29)
2C-T (code 6159) (35)
2C-F (code 6190) (35)
25i-NBOMe (code 6185) (41)
25b-NBOMe (code 6188) (13)
25c-NBOMe (code 6189) (13)

Novel Phenethylamines (continued)

NBOMe: Otherwise Unspecified (code 6203) (13)
TCB-2 (code 6180) (23)
Bromo-DragonFly (code 6176) (25)
DOC (code 6169) (27)
DOB (code 6173) (30)
DOI (code 6168) (30)
DOM (code 636) (32)

Classic Tryptamines

Psilocybin (code 604; variable PSILCY2)

DMT (code 616)

Ayahuasca (code 6103)

Novel Tryptamines

DPT (code 6141) (36)
DiPT (code 6144) (30)
MiPT (code 6140) (38)
4-HO-DET (code 6201) (39)
4-HO-DiPT (code 6175) (42)
4-HO-MET (code 6181) (42)
4-HO-MiPT (code 6179) (38)

Novel Trypamines (continued)

4-AcO-DiPT (code 6177) (22)
4-AcO-DMT (code 6171, 6178) (24)
4-AcO-MET (code 6202) (26)
5-MeO-DALT (code 6183) (28)
5-MeO-DiPT (code 6130) (30)
5-MeO-DMT (code 6061) (32)
5-MeO-MiPT (code 6192) (30)
5-MeO: Otherwise Unspecified (code 6146) (33)

Classic Lysergamides

LSD (code 601; variable LSDFLAG)

Novel Lysergamides

1P-LSD (code 6209) (34)
LSZ (code 6195) (37)
AL-LAD (code 6200) (34)
ALD-52 (code 652) (40)

was classified as a novel lysergamide (code in **Table 1** from variables HALNEWA, HALNEWB, HALNEWC, HALNEWD, HALNEWE = 1) were coded as positive for lifetime novel lysergamide use, whereas those reporting they had never used novel phenethylamines, tryptamines, or lysergamides were coded as negative for lifetime use of those respective compounds. Respondents who responded to the write-in query with "no" and those who did not provide a write-in a response were coded as negative for each of the novel psychedelic use variables. **Supplementary Table 2** presents correlations among lifetime classic and novel phenethylamine, tryptamine, and lysergamide use. It is noted that these correlations ranged from very modest (e.g., lifetime classic phenethylamine use with lifetime novel lysergamide use) to moderate (lifetime classic phenethylamine use with lifetime classic tryptamine use and lifetime classic lysergamide use) to strong (lifetime classic tryptamine use with lifetime classic lysergamide use).

Analysis

Four multivariate logistic regression models were created to test the associations of 1) past month psychological distress (unweighted n = 356,046; variable SPDMON; yes = 1 or no = 0) as measured by the widely-used and well-validated six-item Kessler Psychological Distress Scale (K6; consistent with K6 scoring guidelines and its application in research, the NSDUH uses a dichotomous cutoff score ≥13; 43, 44), 2) past year suicidal thinking (unweighted n = 354,580; "At any time in the past 12 months … did you seriously think about trying to kill yourself? "; variable MHSUITHK; yes = 1 or no = 0), 3) past year suicidal planning (unweighted n = 354,555; "During the past 12 months, did you make any plans to kill yourself? "; variable MHSUITRY; yes = 1 or no = 0), and 4) past year suicide attempt (unweighted n = 354,552; "During the last 12 months, did you try to kill yourself? "; variable MHSUITRY; yes = 1 or no = 0) with the following independent variables: lifetime use of classic phenethylamines (yes = 1 or no = 0), lifetime use of classic tryptamines (yes = 1 or no = 0), lifetime use of classic lysergamides (yes = 1 or no = 0), lifetime use of novel phenethylamines (yes = 1 or no = 0), lifetime use of novel tryptamines (yes = 1 or no = 0), and lifetime use of novel lysergamides (yes = 1 or no = 0; all independent variables were entered simultaneously). Consistent with prior analyses making use of NSDUH data (8, 15), the following covariates were included in the regression models to control for potential sources of confounding: age in years (12–17, 18–25, 26–34, 35–49, 50–64, or 65 or older); sex (male or female); ethnoracial identity (non-Hispanic White, non-Hispanic African American, non-Hispanic Native American/Alaska Native, non-Hispanic Native Hawaiian/Pacific Islander, non-Hispanic Asian, non-Hispanic more than one race, or Hispanic); educational attainment (5th grade or less, 6th grade, 7th grade, 8th grade, 9th grade, 10th grade, 11th grade, 12th grade, freshman college year, sophomore or junior college year, or senior college year or more); annual household income (less than $20,000, $20,000–$49,999, $50,000–$74,999, or $75,000 or more); marital status (married, divorced/separated, widowed, or never married); self-reported engagement in risky behavior ("How often do you like to test yourself by doing something a little risky? "; never, seldom, sometimes, or always); and lifetime use of cocaine, other stimulants, sedatives, tranquilizers, heroin, pain relievers, marijuana, phencyclidine, 3,4-methylenedioxymethamphetamine (MDMA/ecstasy), and inhalants (each aforementioned drug category coded as separate covariates). Logistic regression models were created in R version 3.5.1 using the package "survey" and the svydesign and svyglm functions to account for the complex survey design used by the NSDUH (45, 46), and the package "jtools" to generate 95% confidence intervals and adjusted odds rations for each model (47). Lifetime novel lysergamide use, though quite rare (N = 9 unweighted respondents) was included in the regression models despite the fact that all novel lysergamide users also reported classic lysergamide use. Despite this overlap, multi-collinearity was not present within the model. However, associations of lifetime novel lysergamide use are not reported here given difficulty in interpretation. Indeed, adjusted ORs (all non-significant) revealed values well outside the range of all other variables included in regression models. All of the SPSS syntax, R source code, and datasets used to conduct these analyses are hosted on the Open Science Framework at the following link https://osf.io/xgqmd/.

RESULTS

The weighted frequency of lifetime use of each psychedelic category and lifetime use of specific substances within each of these categories can be found in **Table 2**. As shown in this table, lifetime use of classic psychedelics was much more common than lifetime use of novel psychedelics. Lysergamides were the most commonly used category of classic psychedelic with approximately 10% of the United States population reporting lifetime use, whereas phenethylamines were the most commonly used category of novel psychedelic with one-tenth of one percent of the United States population reporting lifetime use. Psilocybin accounted for the vast majority of those reporting lifetime classic tryptamine use.

Findings generated from the four multivariate logistic regression models can be seen in **Figure 1**. These models show that lifetime classic tryptamine use was associated with a decreased odds of past month psychological distress [adjusted odds ratio or aOR = 0.76; (0.69–0.83)] and past year suicidal thinking [aOR = 0.79; (0.72–0.87)]. Novel phenethylamine use, however, was associated with an increased odds of past year suicidal thinking [aOR = 1.44; (1.06–1.95)] and past year suicidal planning [aOR = 1.60; (1.06–2.41)]. No other significant associations were found.

DISCUSSION

The objective of the present analysis was to test unique population-level associations of classic and novel phenethylamine, tryptamine, and lysergamide use with psychological distress and suicidality, thereby providing one line of evidence regarding which categories of psychedelics might hold the greatest therapeutic potential. We found that lifetime classic tryptamine use, the vast majority of which was accounted for by psilocybin, was associated with a reduced likelihood of past month psychological distress and past year suicidal thinking above and beyond a range of covariates including lifetime use of other classic psychedelics and lifetime use of novel psychedelics. These findings are consistent with a prior

TABLE 2 | Weighted frequencies of lifetime use of each psychedelic category and lifetime use of specific substances within each of these categories from the 2008–2017 NSDUH.

Classic Phenethylamines *(10,332,715; 4.0%)*	**Novel Phenethylamines (continued)**	**Novel Tryptamines (continued)**
		5-MeO-DALT (530; 0.0002%)
Peyote (5,619,308; 2.2%)	DOC (4,994; 0.002%)	5-MeO-DiPT (2,544; 0.001%)
San Pedro (13,513; 0.005%)	DOB (5,181; 0.002%)	5-MeO-DMT (7,889; 0.003%)
Mescaline (8,158,409; 3.1%)	DOI (1,549; 0.0006%)	5-MeO-MiPT (9,383; 0.004%)
Novel Phenethylamines	DOM (16,630; 0.006%)	5-MeO: OU (2,392; 0.0009%)
(277,683; *0.1%)*	**Classic Tryptamines**	**Classic Lysergamides**
	(22,077,615; 8.5%)	*(24,664,123; 9.5%)*
2C-B (119,206; 0.05%)		
2C-C (876; 0.0003)	Psilocybin (22,053,740; 8.5%)	LSD
2C-D (406; 0.0002%)	DMT (252,452; 0.1%)	
2C-E (58,969; 0.02%)	Ayahuasca (52,122; 0.02%)	**Novel Lysergamides**
2C-I (99,203; 0.04%)		*(2,237; 0.0009%)*
2C-P (10,030; 0.004%)	**Novel Tryptamines**	
2C-T-2 (5,158; 0.002%)	*(30,835; 0.01%)*	1P-LSD (153; 0.00006%)
2C-T-7 (7,319; 0.003%)		LSZ (1,370; 0.0005%)
2C-T-21 (1,290; 0.0005%)	DPT (455; 0.0002%)	AL-LAD (248; 0.0001%)
2C-X (0; 0.0%)	DiPT (166; 0.00006%)	ALD-52 (466; 0.0002%)
2C-T (1,400; 0.0005%)	MiPT (0; 0.0%)	
2C-F (124; 0.00005%)	4-HO-DET (1,495; 0.0006%)	
25i-NBOMe (27,020; 0.01%)	4-HO-DiPT (513; 0.0002%)	
25b-NBOMe (2,878; 0.001%)	4-HO-MET (930; 0.0004%)	
25c-NBOMe (4,827; 0.002%)	4-HO-MiPT (357; 0.0001%)	
NBOMe: OU (3,124; 0.001%)	4-AcO-DiPT (0; 0.0%)	
TCB-2 (1,956; 0.0008%)	4-AcO-DMT (7,141; 0.003%)	
Bromo-DragonFly (1,598; 0.0006%)	4-AcO-MET (252; 0.0001%)	

Frequencies reported here are formatted as such: (weighted N's; weighted %'s of total US population; OU, Otherwise Unspecified).

analysis indicating that lifetime psilocybin use may be especially protective against psychological distress and suicidality as compared to other classic psychedelics (9). Results were also consistent with a number of recent clinical trials suggesting that psilocybin is a promising therapeutic agent for end-of-life anxiety, treatment-resistant depression, alcohol dependence, and tobacco dependence (3, 4, 48–50). It is noted that though very few respondents reported lifetime use of ayahuasca, recent clinical trials suggest a substantial and rapid antidepressant effect of this DMT-containing admixture (51, 52). It may be, therefore, that classic tryptamines are among the most promising therapeutic agents of the psychedelics.

Sexton et al. found that lifetime use of novel psychedelics increased the likelihood of past year suicidal thinking and planning compared to lifetime classic psychedelic use only (15). In the present study, we found that novel phenethylamine use was associated with an increased likelihood of past year suicidal thinking and planning above and beyond several covariates including lifetime use of classic psychedelics and lifetime use of other novel psychedelics. Lifetime use of novel tryptamines was not associated with psychological distress or suicidality. The same was true of novel lysergamides, though interpretation of this finding is complicated by very few respondents reporting the use of novel lysergamides and the fact that all novel lysergamide users also reported the use of classic lysergamides. Nevertheless, this suggests that novel phenethylamine use accounts for the prior associations of Sexton et al., and that novel phenethylamines may be, to some degree, potentially harmful to mental health (15). Indeed, there have been a number of adverse event reports from novel phenethylamine use including psychosis, neurovascular hemorrhages, and seizures (53–56). These findings support the conclusion that novel phenethylamine psychedelics may be distinct from other psychedelic categories in that they may confer harm.

Tryptamine-based compounds in general have affinity for and agonist activity at primarily several different serotonin receptors. For example, psilocin, the active metabolite of the prodrug classic tryptamine psychedelic psilocybin, has varying but appreciable affinity for all serotonin receptors, with the exception of the 5-HT_3 receptor, where it acts as an agonist, and the 5-HT_7 receptor, where it is an antagonist. Significantly, all known tryptamines that have been tested have affinity for and agonist activity at 5-HT_{1A} receptors. Activation of this receptor has been associated with antidepressant activity, and proposed as an important mechanism of the antidepressant effects of selective serotonin reuptake inhibitor medications (57, 58). Indeed, new antidepressant medications on the market were specifically designed to have at least partial agonist activity at 5-HT_{1A} receptors (59). It is possible that activation of 5-HT_{1A} receptors within the brain by classic tryptamine psychedelics confers positive effects to affective states and the observed reduction of psychological distress and suicidality in users. This may also apply to novel tryptamine psychedelics, though lifetime use of novel tryptamine psychedelics was not associated with psychological distress or suicidality in the current study, perhaps due to a lack of statistical power.

The phenethylamine compounds listed in **Table 2**, especially the novel phenethylamine 2C class, more often have affinity for and activity at the alpha-adrenergic receptor as well as moderate

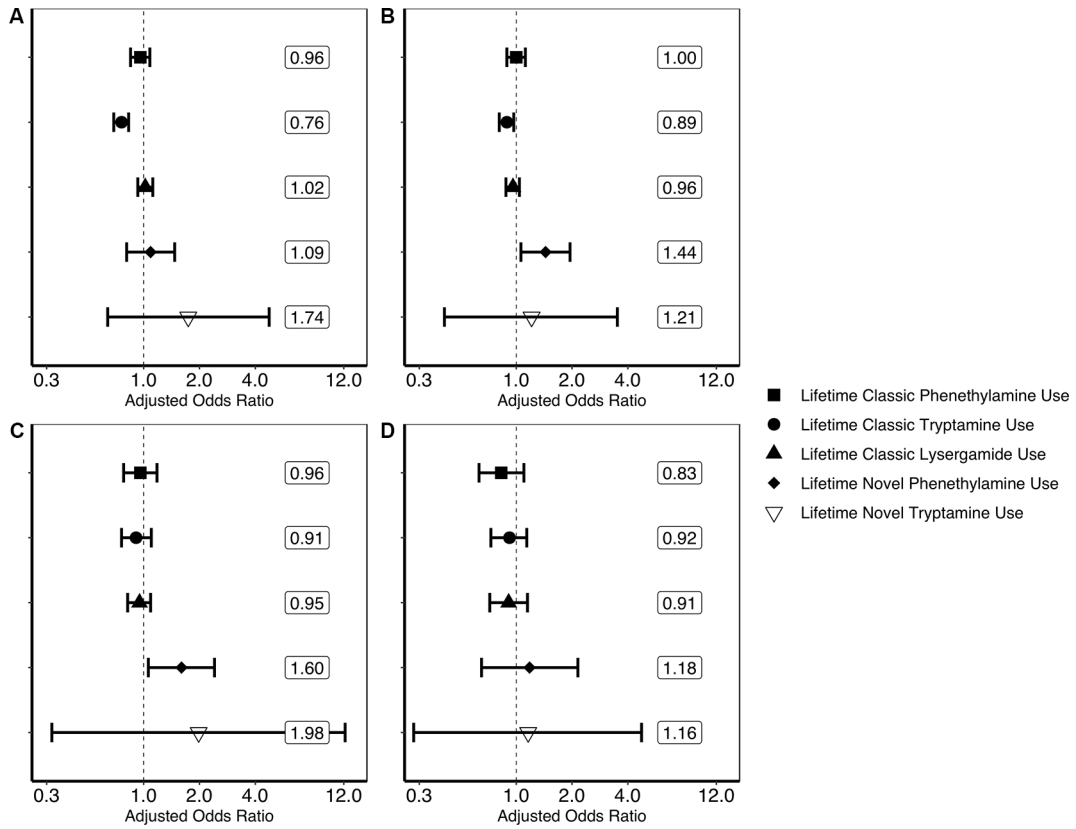

FIGURE 1 | Results of multivariate logistic regression models predicting past month psychological distress and past year suicidality. **(A)** Result of multivariate logistic regression model predicting past month psychological distress (unweighted *n* = 356,046). **(B)** Result of multivariate logistic regression model predicting past year suicidal thinking (unweighted *n* = 354,580). **(C)** Result of multivariate logistic regression model predicting past year suicidal planning (unweighted *n* = 354,555). **(D)** Result of multivariate logistic regression model predicting past year suicide attempt (unweighted *n* = 354,552). Each plotted shape relates to the drug category and represent weighted adjusted odds ratio point estimates and error bars are 95% confidence intervals. Associations are adjusted for the following covariates: age in years (12–17, 18–25, 26–34, 35–49, 50–64, or 65 or older); sex (male or female); ethnoracial identity (non-Hispanic White, non-Hispanic African American, non-Hispanic Native American/Alaska Native, non-Hispanic Native Hawaiian/Pacific Islander, non-Hispanic Asian, non-Hispanic more than one race, or Hispanic); educational attainment (5th grade or less, 6th grade, 7th grade, 8th grade, 9th grade, 10th grade, 11th grade, 12th grade, freshman college year, sophomore or junior college year, or senior college year or more); annual household income (less than $20,000, $20,000–$49,999, $50,000–$74,999, or $75,000 or more); marital status (married, divorced/separated, widowed, or never married); self-reported engagement in risky behavior ("How often do you like to test yourself by doing something a little risky?"; never, seldom, sometimes, or always); and lifetime use of cocaine, other stimulants, sedatives, tranquilizers, heroin, pain relievers, marijuana, phencyclidine (PCP), 3,4-methylenedioxymethamphetamine (MDMA/ecstasy), and inhalants (each aforementioned drug category coded as separate covariates). Associations of covariates with psychological distress and suicidality are not reported here. The associations of lifetime novel lysergamide use are not evaluated here as noted in the *Discussion*.

affinity for blockade of norepinephrine and dopamine transporters, whereas most tryptamines do not (60–63). Further, there is little to no activation of 5-HT_{1A} receptors by these drugs. Together, activation of alpha adrenergic receptors with increases in synaptic norepinephrine and dopamine would be predicted to induce behavioral outcomes similar to amphetamines, including negative effects on cognitive behavioral control (64). These pharmacological outcomes, predicted to occur more frequently with phenethylamine (and especially the novel 2C phenethylamine) drugs than tryptamines, could underlie the observed associations of these novel phenethylamines with negative psychological health. In support of this view, 2C-B, the most commonly reported novel phenethylamine, is often substituted for MDMA among electronic music party goers secondary to its purported psychostimulant properties (15, 20, 65). Indeed, novel phenethylamines are often described in terms of psychostimulant effects (20, 29), whereas challenging, emotional breakthrough, and mystical-type experiences appear to underlie the therapeutic outcomes of the classic tryptamine psychedelic psilocybin (16, 66, 67). Thus, with regard to acute subjective effects, it may be that novel phenethylamines are characterized more so by problematic psychostimulant outcomes and less so by salubrious challenging, emotional breakthrough, and mystical-type experiences. It is important to interpret these associations with caution, however, as the NSDUH only provides data on naturalistic psychedelic use and it is quite possible that certain novel phenethylamines hold therapeutic potential when administered in a controlled environment.

A strength of the current study includes the assessment of a large, nationally representative sample of respondents from real-

world settings. Additionally, the code used to conduct these analyses and the data sets that were analyzed are freely available online on the Open Science Framework. As in prior analyses, this analysis used a range of covariates to control for a number of sources of confounding (8, 9, 15). Furthermore, when estimating the associations of one independent variable (e.g., lifetime classic tryptamine use), our models controlled for the other five independent variables (e.g., lifetime classic phenethylamine use, lifetime classic lysergamide use, lifetime novel phenethylamine use, lifetime novel tryptamine use, and lifetime novel lysergamide use). Despite this approach, a number of limitations should be noted. First, an obvious limitation is reliance on self-report, which may have obfuscated true relationships between classic and novel psychedelic use and mental health outcomes. Second, as with any population-based survey, we could not control for every possible source of confounding. Any number of unassessed covariates may account for the associations reported here. For instance, perhaps classic tryptamine users are especially open to new experience and spiritual, and therefore the reported associations reflect the influence of these traits, rather than an effect of classic tryptamine use. Moreover, novel phenethylamine users may be especially prone to neuroticism, and therefore associations with suicidal thinking and planning may capture the impact of this characteristic on these outcomes (see 8). As noted above, the novel phenethylamine 2C-B may have a reputation as a "party drug, " and thus the associations reported here may reflect the influence of recreational use motives. One such motive may be sensation seeking (see 68–71) which can be defined as a trait characterized by "the seeking of varied, novel, complex, and intense sensations and experiences, and the willingness to take physical, social, legal, and financial risks for the sake of such experience" (72, page 27). Though the inclusion of self-reported engagement in risky behavior as a covariate in analyses likely accounted for some of the variance in this trait, sensation seeking itself, in addition to a number of other relevant psychological constructs (e.g., openness and neuroticism), was not assessed by the NSDUH. In any event, as with any cross-sectional survey, the present results may not necessarily indicate causation. Third, as analyses were restricted to the available data (i.e., whether or not a respondent had used a classic or novel phenethylamine, tryptamine, or lysergamide psychedelic in his or her lifetime), dose-response relationships as well as associations with frequency of use, age of first use, recency of use, and any number of other variables pertaining to use patterns could not be tested. Future surveys including the NSDUH that seek to better understand the relationships of psychedelic use with mental health would benefit from the assessment of more complex use patterns rather than simple lifetime use. Additionally, there was overlap among lifetime classic and novel phenethylamine, tryptamine, and lysergamide psychedelic use, which might have limited the ability to detect the unique associations of these predictor variables with the outcomes (e.g., lifetime classic lysergamide use might be associated with a reduced likelihood of psychological distress and suicidality, but not above and beyond lifetime classic tryptamine use, with which it was strongly correlated). Fourth, population-level associations may obscure effects at the individual level. Thus, despite the reported trends, it is possible that some individuals were harmed by classic tryptamine use, whereas others benefited from novel phenethylamine use. Finally, as noted in Sexton et al., the write-in nature of lifetime novel psychedelic use likely lead to underreporting of these substances, which potentially affected the current estimates, including limiting power to detect associations (15). This is especially true in the case of lifetime novel lysergamide use (N = 9 unweighted respondents), where all lifetime novel lysergamide users reported lifetime classic lysergamide use. It is quite possible that data from surveys with predetermined items assessing novel psychedelic use would yield different findings.

CONCLUSIONS

The present research suggests that classic tryptamine psychedelics (i.e., ayahuasca, DMT, and psilocybin) may hold the greatest therapeutic potential of the psychedelics in that lifetime use of these substances was uniquely associated with a decreased likelihood of psychological distress and suicidal thinking. Novel phenethylamines, by contrast, might be distinct from other psychedelics in that lifetime use of these substances was independently associated with an increased likelihood of suicidal thinking and planning. Of course, the present data are by no means definitive, and it is possible that the range of psychedelic substances have clinical utility. Nevertheless, as clinical research with psychedelics remains in its infancy, the current study points to classic tryptamines as the best candidates for further study, with novel phenethylamines posing the potential for harm. Future research should aim to combine population-level methodology with chemical and pharmacological data to further investigate the therapeutic potential of classic and novel phenethylamine, tryptamine, and lysergamide psychedelics.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are available on the Open Science Framework at the following link: https://osf.io/xgqmd/.

AUTHOR CONTRIBUTIONS

JS was the primary author who cleaned data, conducted analyses and drafted the manuscript summarizing the findings. CN contributed meaningful pharmacological expertise to inform methodology and aid in the interpretation of results. PH, corresponding author, was responsible for ensuring analyses were conducted and interpreted correctly.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00896/full#supplementary-material

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Learning to Let Go: A Cognitive-Behavioral Model of How Psychedelic Therapy Promotes Acceptance

Max Wolff[1,2,3]*, *Ricarda Evens*[4], *Lea J. Mertens*[5], *Michael Koslowski*[4], *Felix Betzler*[4], *Gerhard Gründer*[5] *and Henrik Jungaberle*[3]

[1] Faculty of Psychology, Technische Universität Dresden, Dresden, Germany, [2] Department of Psychiatry and Psychotherapy, Technische Universität Dresden, Dresden, Germany, [3] MIND Foundation, Berlin, Germany, [4] Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Berlin, Germany, [5] Department of Molecular Neuroimaging, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

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***Correspondence:**
Max Wolff
max.wolff@tu-dresden.de

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The efficacy of psychedelic-assisted therapies for mental disorders has been attributed to the lasting change from experiential avoidance to acceptance that these treatments appear to facilitate. This article presents a conceptual model that specifies potential psychological mechanisms underlying such change, and that shows substantial parallels between psychedelic therapy and cognitive behavioral therapy: We propose that in the carefully controlled context of psychedelic therapy as applied in contemporary clinical research, psychedelic-induced belief relaxation can increase motivation for acceptance *via* operant conditioning, thus engendering episodes of relatively avoidance-free exposure to greatly intensified private events. Under these unique learning conditions, relaxed avoidance-related beliefs can be exposed to corrective information and become revised accordingly, which may explain long-term increases in acceptance and corresponding reductions in psychopathology. Open research questions and implications for clinical practice are discussed.

Keywords: psychedelic therapy, cognitive behavioral therapy, avoidance, acceptance, psilocybin, lysergic acid diethylamide, ayahuasca

INTRODUCTION

In recent years, several early-phase clinical trials have provided evidence that classic serotonergic psychedelics—in most cases psilocybin, but also lysergic acid diethylamide (LSD) and the dimethyltryptamine (DMT)-containing brew ayahuasca—may occasion substantial and often sustained symptom reductions in patients treated for depression (1–3), psychological distress related to life-threatening illness (4–8), obsessive-compulsive disorder (9), and substance use disorders (10, 12). It has been proposed that psychedelic therapy works by reducing patterns of *experiential avoidance* and promoting more adaptive *acceptance* [(13); see below for definitions of these terms]. However, it remains largely unclear how psychedelic therapy may produce such change. Taking the perspective of cognitive behavioral therapy (CBT), and building on the recently proposed relaxed-beliefs account of psychedelics' acute brain action (14), the present article aims to

clarify the psychological mechanisms underlying the acceptance-promoting effects of psychedelic therapy. We propose a conceptual model describing how psychedelic-induced belief relaxation, when combined with specific context factors that are typically present in psychedelic therapy, can facilitate the same acceptance-promoting learning process as that targeted by CBT interventions. In the following, we introduce the concepts of avoidance and acceptance, outline how CBT aims to promote acceptance, and review evidence that psychedelic therapy also promotes acceptance. We then briefly introduce the relaxed-beliefs account and, based on this, present our conceptual model of how psychedelic therapy promotes acceptance. This is followed by a discussion of open research questions and implications for clinical practice.

Promoting Acceptance in Cognitive Behavioral Therapy

Many symptoms of mental disorders can be interpreted in terms of avoidance. This is most obvious in anxiety disorders, where avoidance of anxiety-provoking situations is a cardinal symptom, but it is also the case for many other diagnostic categories (15, 16): In depression, passivity, withdrawal, and rumination may serve to avoid unwelcome emotional experiences (17–20). In substance use disorders, intoxication may serve a similar purpose (21). In obsessive-compulsive disorder, washing rituals may neutralize worries about contamination (22), etc. When viewed as avoidance strategies, all these behaviors "work" in the sense that they diminish the threat of aversive experiences in the very short run. However, this small benefit comes at the immense longer-term cost of constraining the individual's personal liberty and perpetuating the disorder.

While the relevance of avoidance in psychopathology is recognized by all major schools of psychotherapy (23), it is especially emphasized in the so-called third wave of CBT. Here, experiential avoidance—defined as the attempt to evade, escape, or otherwise alter *private events* (i.e., emotions, thoughts, memories, body sensations, etc.) despite harmful long-term consequences—is considered a central factor underlying the development and maintenance of a wide range of psychopathologies (23, 24). Acceptance refers to the converse ability to allow private events to unfold without attempting to control them. Acceptance thus relates closely to the concept of mindfulness (25) and is considered a core mechanism of positive behavior change in third-wave CBTs such as dialectical behavior therapy [DBT; (26)], mindfulness-based cognitive therapy [MBCT; (27)], and acceptance and commitment therapy [ACT; (28)]. Beyond these "acceptance-based" approaches, CBT emphasizes the role of avoidance in anxiety disorders, but seeks to reduce harmful behaviors, including maladaptive patterns of avoidance, across diagnostic boundaries.

To facilitate lasting change from experiential avoidance to acceptance, cognitive-behavioral therapists use interventions aimed at different interdependent aspects of an acceptance-promoting learning process (see **Figure 1**). On a cognitive level, CBT seeks to enable the revision of avoidance-related beliefs, i.e., belief structures that motivate (and are sustained by) experiential avoidance. These may involve rather implicit negative expectancies

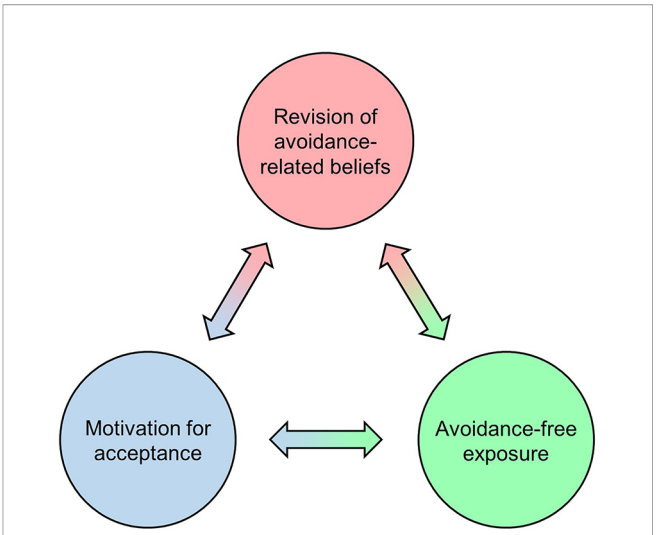

FIGURE 1 | Interdependent cognitive, behavioral, and motivational aspects of an acceptance-promoting learning process. CBT aims to facilitate this learning process in order to promote lasting change from experiential avoidance to acceptance.

(29) as well as preconscious assumptions and more explicit convictions about private events (e.g., "Anxiety is dangerous"), related self-conceptualizations (e.g., "I cannot handle anxiety"), and corresponding rules (e.g., "I must avoid anxiety at all costs"). Verbal interventions aimed at facilitating the revision of such beliefs can focus on changing either their content or functional impact on behavior, and may involve disputation *via* Socratic dialogue (30), metaphors (31), decentering or psychological distancing (32), defusion exercises (31), etc.

On a behavioral level, avoidance-free exposure is applied to induce corrective experiences with otherwise avoided private events. A prototypical case of exposure treatment is applied in classical CBT of anxiety disorders, which aims to reduce conditioned fear *via* extinction learning, i.e., by repeatedly confronting the patient with fear-provoking stimuli in the absence of aversive outcomes (33). Exposure in the form of behavioral experiments, i.e., gentle confrontation with avoided experiences to revise avoidance-related beliefs, is also applied beyond anxiety disorders [e.g., in depression; (34)]. Acceptance-based CBTs commonly pursue exposure through mindfulness-based exercises, which resemble classical exposure treatment of anxiety disorders in that a stimulus (in this case private events such as emotions, thoughts, memories, or body sensations) is openly attended to while desisting from avoidant responses (25, 27, 35). The similarity between mindfulness and other exposure treatments is reflected in that regular mindfulness exercise structurally and functionally affects the same network of brain regions that is also assumed to support fear extinction (36, 37), suggesting that this type of "internal" exposure can reduce avoidance *via* the extinction of threat responses to private events. Note that these events may still be unpleasant or painful even when they are no longer experienced as threatening. After all, acceptance-based CBTs do not primarily

aim to change the form or frequency of aversive experiences, but to reduce harmful patterns of experiential avoidance (38).

On a motivational level, exposure is typically impeded by the fact that avoidant responses have been conditioned through reinforcement learning: As illustrated by the introductory examples above, avoidance often leads to immediate reductions in aversion. This negative reinforcement (i.e., removing an aversive stimulus or preventing an aversive event from happening) strengthens the avoidant response, meaning it will subsequently tend to occur with higher frequency, longer duration, greater magnitude, and/or shorter latency. By contrast, negative consequences of avoidance typically unfold much more slowly, and thus have little impact on operant learning. CBT seeks to counteract conditioned avoidance by increasing the patient's readiness to engage with aversive experiences (39), i.e., by building motivation for acceptance. This can be done by promoting insight into the longer-term costs of avoidance agendas (40), particularly with respect to their incompatibility with personally valued goals (38), and may involve motivational interviewing techniques (41). Likewise, avoidance motivation can be reduced through metaphors and experiential methods that demonstrate negative consequences or the futility of avoidance (38).

Avoidance and Acceptance in Psychedelic Therapy

Psychedelic therapy refers to treatments for mental disorders where the patient is administered between one and a few moderate or high doses of a classic serotonergic psychedelic (psilocybin, LSD, or ayahuasca) under carefully controlled conditions in a professional clinical setting (42). During dosing sessions, which are embedded in a brief intervention model with preparatory and integrative counseling sessions, therapists usually take a non-directive approach. The patient, who is encouraged to turn attention inward, is mostly lying down, wearing eyeshades, and listening to a carefully selected playlist of music over headphones as the acute psychedelic experience unfolds [for concise summaries of the phenomenology of psychedelic states see (42, 43)].

There is mounting evidence that the positive long-term effects of psychedelic therapy are mediated by the quality of the acute psychedelic experience (44–47). Qualitative interviews with patients have shown that avoidance and acceptance are often central themes of their psychedelic experiences (13, 48–51), and patients commonly report transient episodes of struggle with intense aversion. These *challenging experiences*[1] (42, 52, 53) are often characterized by extreme fear or panic, and can involve frightening imagery, unsettling body sensations, and the apprehension of immediate threat. This is the case even though patients are usually aware of their physical safety and the transitory nature of the experience. Attempts to exert control over challenging experiences (i.e., experiential avoidance) typically fail to bring the intended relief. Instead, patients frequently report that the experience only—and often immediately—assumed a more positive character when they eventually "surrendered" or "let go", i.e., when they adopted an accepting attitude. The associated experience of an *emotional breakthrough* is commonly described as insightful and rewarding, and has been proposed to constitute a key component of psychedelic therapy (13, 54). Patients often experience episodes of unique openness to greatly intensified emotions during dosing sessions, and commonly describe the sensation that previously "hidden" or "suppressed" feelings became "accessible" or were "released" (13, 48, 49). Many patients report increases in emotional openness that last long after acute drug effects subside (13), and symptom reductions after psychedelic therapy are associated with enhanced neural measures of emotional responsiveness (55, 56). This is in line with quantitative evidence for lasting psychedelic-induced increases in the personality trait openness to experience (a negative correlate of experiential avoidance; 57) observed in clinical (58) and non-clinical samples (59–61). Psychedelic therapy thus appears to promote lasting change from experiential avoidance to acceptance (13). It has been proposed that this effect is causally related to the mentioned emotional breakthrough experiences, and a recent survey study lends preliminary support to this view (54). However, the underlying psychological processes have not been specified so far. Further below, we will present a conceptual model according to which psychedelic therapy can facilitate the same acceptance-promoting learning process as that targeted by CBT interventions (**Figure 1**). We base this argument on the recently proposed relaxed-beliefs account of the acute brain action of psychedelics (14).

The Relaxed-Beliefs Account of Psychedelics' Acute Brain Action

Carhart-Harris and Friston (14) proposed a unified account of the acute brain action of psychedelics. Although this recent theory still requires further empirical support, it widely accommodates the current state of knowledge about these substances' psychopharmacology, and parsimoniously explains their various psychotropic effects as the result of psychedelic-induced belief relaxation. The theory's neurobiological and information theoretical details are beyond the scope of this article, but understanding belief relaxation sufficiently to follow our argument requires a basic concept of *predictive processing*, arguably the leading unified account of brain and mind function (62, 63). According to the predictive processing framework, the brain with its hierarchical architecture entertains a hierarchically organized generative model of the current and general state of the world. At lower levels in the hierarchy, this model comprises rather momentary hypotheses about the causes of current sensory inputs (e.g., the perceptual belief that one is looking at a tree). At higher levels, the model becomes increasingly abstract, and forms more enduring hypotheses about the general nature of the world. At the highest levels, far removed from the sensorium, these beliefs (which do not need to be consciously held) are usually highly stable, such as the belief that a self exists and has certain properties.

To fulfill its biological function and control adaptive behavior in a complex changing environment, the brain needs the ability to form new beliefs and change existing ones. This ongoing process of

[1]Contrasting the colloquial "bad trip", this intentionally neutral term accommodates the possibility that these experiences may in fact, as discussed below, be therapeutically valuable.

belief updating is assumed to be guided by the principle of prediction error minimization: At each level of the hierarchy, probabilistic top-down predictions based on current beliefs are continuously compared with bottom-up inputs (basic sensory information at the lowest levels), and beliefs are adjusted in such a way that prediction errors (mismatches between predictions and inputs) are minimized. This process underlies the flexibility of the generative model, and ensures its correspondence with the external world. However, the sensitivity of beliefs toward ascending prediction errors may vary. Heavily-weighted (i.e., insensitive or "confident") high-level beliefs are not easily updated, and often exert far-reaching constraining effects: They suppress prediction errors from certain lower-level parts of the model and keep them from impressing on higher levels. Thereby, these so-called compressive beliefs give the model stability and drastically reduce the number of its possible states, thus constraining phenomenal experience. For instance, the experience of seeing sounds (a case of visual-auditory synesthesia) should be largely prevented by heavily-weighted compressive beliefs along the lines of "sound is invisible" (the default state for non-synesthetes in normal waking consciousness).

The relaxed-beliefs account states that psychedelics acutely reduce the weight (i.e., confidence) of higher-level beliefs: By increasing their sensitivity toward prediction errors, otherwise stable beliefs become more easily updated. Furthermore, bottom-up information that is normally inhibited by compressive beliefs becomes liberated and is allowed to "travel up the hierarchy with greater latitude and compass" (14). This leads to a less constrained, more flexible state of mind which the authors refer to as the "anarchic brain". A central characteristic of this state is increased context sensitivity, i.e., a heightened susceptibility toward ongoing processes in the internal and external context [or "set" and "setting"; see (64, 65)]. Processing domains which under normal circumstances are largely kept apart thus become more strongly interconnected. As a result, context-sensitivity phenomena like visual-auditory synesthesia (i.e., sensitivity of visual processes toward the auditory processing context, reflecting the relaxation of beliefs such as "sound is invisible") are characteristic of psychedelic states. Beyond that, belief relaxation arguably accounts for the full spectrum of subjective phenomena associated with the psychedelic experience, including not only perceptual alterations but also visionary experiences, emotional lability, noetic insight, compromised sense of self, etc.

A COGNITIVE-BEHAVIORAL MODEL OF HOW PSYCHEDELIC THERAPY PROMOTES ACCEPTANCE

In this section, we describe some possible corollaries of belief relaxation that, in our view, can explain how psychedelic therapy promotes lasting change from experiential avoidance to acceptance: operant conditioning of acceptance, the elicitation and intensification of private events, and the relaxation of avoidance-related beliefs. According to our conceptual model (**Figure 2**), synergies between these psychedelic-therapy-specific factors can facilitate the same acceptance-promoting learning process as that targeted by CBT interventions.

Operant Conditioning of Acceptance

A central cause of the stability of pathological avoidance is, as previously mentioned, that avoidant responses have often been repeatedly strengthened by negative reinforcement. It appears that this circumstance can be essentially reversed in psychedelic therapy, with the result that acceptance is conditioned instead of avoidance. Consider the following report of a psychedelic experience by a patient treated with psilocybin for depression:

> *There was this huge terrifying creature with a rifle, and instead of running away, I looked at it, and it wasn't as scary as it had seemed. [My] fear subsided, it suddenly seemed ridiculous, I started laughing. If I had avoided it, it would have got more terrifying.*
>
> Patient #4 (13)

Here, the patient's curious, accepting response to an aversive aspect of the experience (looking at the terrifying creature instead of running away) is negatively reinforced (the creature appearing less scary). Moreover, the patient has apparently somehow learned that an avoidant response (running away) would have been punished (the creature becoming even more terrifying). In what follows, we show that psychedelic-induced belief relaxation can account for such operant conditioning of acceptance.

Avoidance Sensitivity

As explained above, belief relaxation is thought to produce a relatively unconstrained state of mind characterized by increased sensitivity to context. This context sensitivity should emerge not only within perception (e.g., synesthesia between visual and auditory processes) but also between perceptual and affective-motivational processes. In the anarchic brain, increased bottom-up information flow from limbic into higher cortical areas (14) may allow avoidance-related processes to infiltrate and distort perception in ways that resemble synesthetic phenomena. Hence, avoidant states may bias perceptual belief updating towards what is (innately or by learning) associated with avoidance, leading to the emergence of threat-related perceptual content. For instance, the attempt to suppress a certain emotion may give rise to (more) unpleasant body sensations or repulsive imagery. The psychedelic state may thus involve a feedback loop whereby avoidant responses to aversive private events tend to increase aversion. We refer to this presumed circumstance as *avoidance sensitivity*, and propose that it constitutes a vital factor in psychedelic therapy.

Due to avoidance sensitivity, psychedelic states may be characterized by an intrinsic tendency to punish avoidance and reward acceptance. To prevent misunderstandings, this should not mean that avoidant behaviors always increase aversion in psychedelic states. For instance, physically escaping from a threatening external stimulus may in fact often be rewarded by decreased fear and feelings of relief (due to removal of the stimulus). We assume that punishment of avoidance *via* avoidance sensitivity is most likely to occur when avoidance is directed toward private events that are relatively unrelated to the immediate stimulus environment, i.e., in introspection as is

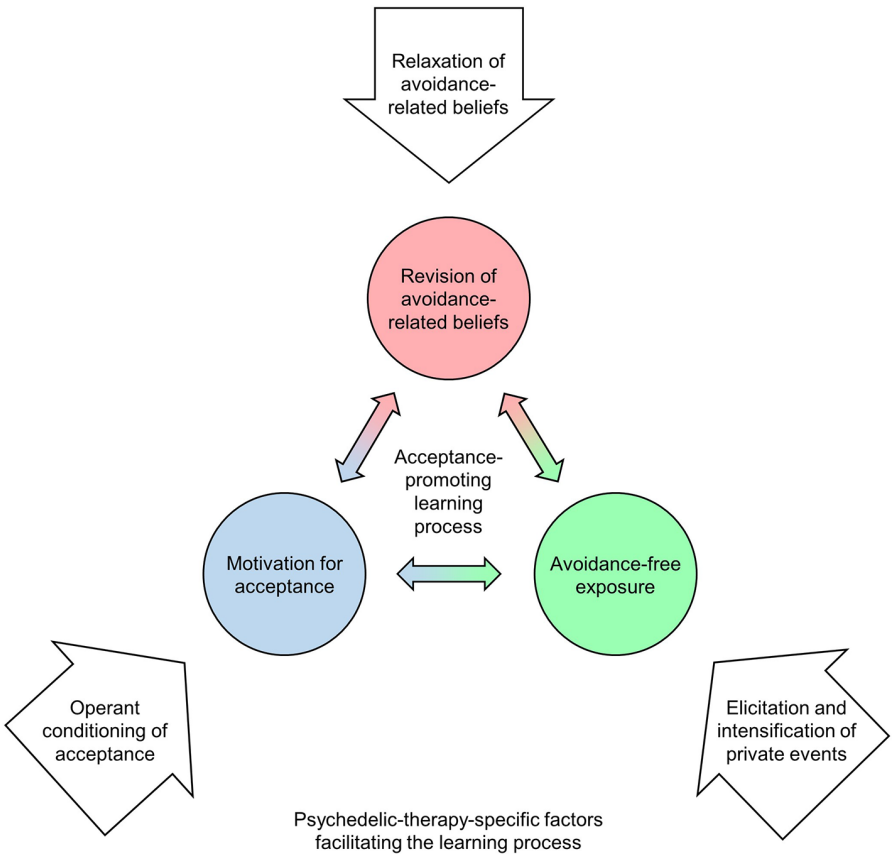

FIGURE 2 | The proposed cognitive-behavioral model of how psychedelic therapy promotes acceptance. According to the model, psychedelic therapy facilitates the same learning process as that targeted by CBT interventions (see **Figure 1**). The proposed psychedelic-therapy-specific factors (white arrows) are assumed to arise from synergies between psychedelic-induced belief relaxation (14) and the particular context that is established according to psychedelic therapy protocols employed in contemporary research.

encouraged in psychedelic therapy. Here, covert avoidance (e.g., trying to suppress aversive visual imagery by imagining something else) may produce more aversive content than it can eliminate. This is presumably intensified by additional context factors that are usually present in psychedelic therapy, where the patient is mostly lying down and wearing eyeshades. The resulting uncertain stimulus environment and associated deprivation from the grounding influence of well-defined sensory input (the notable exception being auditory stimulation with music, which is discussed below) can be assumed to strongly increase hallucinatory aspects of the psychedelic experience (66), and thus amplify avoidance sensitivity. This should be further enhanced by the patient's lying-down body position, as reduced movement forbids many uses of active inference [i.e., acting on the environment to reduce uncertainty; (67)].

Shaping Acceptance

Given that avoidance sensitivity is presumably affected by the stimulus environment, the patient may use overt avoidance behaviors (removing the eyeshades, getting up and moving around, etc.) to seek distraction and tune down the intensity of aversive experiences. Such strategies, which can be actively supported by therapists, may in fact often reduce aversion to some degree. Nevertheless, due to encouragement by therapists and information provided in preparatory sessions, the patient may try and continue within introspection. Initial attempts at engaging with challenging experiences will likely reflect the patient's habitual patterns of responding, and may often rely on what has previously "worked" in everyday life: experiential avoidance. However, due to avoidance sensitivity, the attempt to exert control over the flow of events will likely aggravate aversive features of the experience, which may, in turn, elicit an even stronger avoidant response. Such escalation can be expected to proceed until the patient either resorts to overt avoidance or begins to desist from avoidance altogether. If neither occurs, the patient may soon find themselves in an intensely aversive state of panic[2].

As soon as the patient spontaneously shows a minimum of acceptance toward an aversive aspect of the experience, this may initiate an operant process that can be described as an automatic

[2]The described process bears some resemblance to the escalation of anxiety in panic attacks, which is assumed to be driven by catastrophic misinterpretation of (and associated avoidant responses to) body sensations (68).

form of shaping[3]. At first, the patient may only partially refrain from avoidance. Such a nuanced change in set may noticeably attenuate the emergence of threat-related perceptual content, thereby slightly reducing aversion. In the above example, as little as one curious glance at the terrifying creature (instead of, for instance, thinking about how to best run away from it) could already have made it appear significantly less frightening. Strengthened by such negative reinforcement, the initially only partial acceptance may subsequently generalize. Avoidance strategies are then increasingly let go of, and acceptance is brought to additional aspects of the experience. Here, broader acceptance can be assumed to yield stronger reinforcement. Under favorable conditions, this may allow the patient to rapidly achieve high levels of acceptance, even toward types of private events that are otherwise strongly avoided. The common phenomenon that a challenging psychedelic experience is suddenly resolved in a moment of breakthrough (54) could be explained as the result of such rapid shaping-like processes.

Certain additional context factors that are commonly present in psychedelic therapy (42) can be assumed to be crucial for the described process: The importance of assuming an accepting attitude toward the psychedelic experience is explicitly explained to the patient in preparatory sessions. The patient is instructed accordingly, and is encouraged to set an intention to "trust, let go, and be open" (70). Furthermore, therapists may serve as models for acceptance throughout the treatment, and may cue acceptance to the patient in dosing sessions. Patients have also attributed increases in acceptance of challenging psychedelic experiences to the encouraging influence of music (71). Not least, the purposefully created atmosphere of support, safety, and trust should be considered necessary for acceptance to be learned in psychedelic therapy.

Elicitation and Intensification of Private Events

> *Excursions into grief, loneliness and rage, abandonment. Once I went into the anger it went 'pouf' and evaporated.*
>
> Patient #3 (13)

Such reports of exceptional openness to previously "hidden" or "suppressed" feelings during dosing sessions (13, 48, 49) suggest that conditioned acceptance may yield unique opportunities for exposure to private events that are otherwise avoided. Apart from the necessity to desist from avoidant responses, successful exposure treatment requires that suitable exposure targets (i.e., avoidance-related private events that are meaningfully related to the patient's psychopathology) are elicited and experienced with sufficient intensity. Hence, it appears advantageous that psychedelic-induced belief relaxation should involve the dissolution of top-down constraints on emotional, mnemonic, and perceptual processes (14). The resulting emotional effects, including the intensification of feelings, increased conscious access to emotions, and broadening of emotional range (43), may be of particular therapeutic value in this regard.

Considering that dosing sessions in psychedelic therapy usually last several hours, one might assume that the long duration alone ensures that therapeutically valuable exposure targets will sooner or later emerge. Furthermore, it is possible that the patient simply knows where in life avoidance is harming them [this could be further facilitated by the insight-promoting effects of belief relaxation; (14)], and actively engages with the respective topics. However, patients sometimes report a sense of being drawn into or guided towards "necessary" experiences, bearing the notion of an "inner therapist" (13), and suggesting that some highly efficient involuntary process of exposure target selection may be at work. It is an interesting possibility that such a process could be driven by periodic returns to avoidant responding (in behaviorist terms: *resurgences*): When an avoidant set is (re-)established for a brief moment, perceptual belief updating should be transiently biased towards what is associated with avoidance in the individual's memory. Thereby, periodic resurgences of avoidance may somewhat inevitably direct the flow of private events to what the patient most vigorously avoids in everyday life—which will likely relate to their individual psychopathology. Although speculative at present, it is conceivable that the surfacing of "forgotten" emotional memories [a regular occurrence in psychedelic therapy; (42)] and other phenomena that patients may attribute to an inner therapist would be facilitated by such a mechanism.

In the controlled context of psychedelic therapy, it can be expected that sensory deprivation in the visual, tactile, and proprioceptive domains will enhance the elicitation and intensification of private events. Another context factor of particular importance is music (72): Music increases psychedelic-induced visual imagery, which then often involves autobiographical memories (73), and can interact with self-referential processing in such a way that the personal meaningfulness of psychedelic experiences is increased (74). Perhaps most importantly, music's powerful ability to evoke and amplify emotions is greatly enhanced in psychedelic states (71, 75, 76). Due to its central role in psychedelic therapy as a source of emotionality and meaning, music has been metaphorically referred to as "the hidden therapist" (72).

Relaxation of Avoidance-Related Beliefs

Patterns of pathological avoidance are, as explained above, sustained by avoidance-related beliefs that motivate avoidant behavior and thereby impede corrective experiences. In terms of predictive processing, such rigid pathological beliefs are characterized by excessive weight (confidence), i.e., strong suppression of bottom-up information and insensitivity to prediction errors. In line with the notion that psychedelic therapy works by making rigid pathological belief systems malleable (14), we propose that the relaxation of avoidance-related beliefs opens a temporary window of plasticity through which these beliefs may undergo revision. However, this by itself should not warrant that avoidance-related beliefs are really changed, let alone with beneficial results. From a CBT

[3] Shaping is a conditioning paradigm where the subject's spontaneous behavior is gradually changed towards a target behavior by differential reinforcement of successive approximations (69).

perspective, positive results should be expected only when prediction errors encountered under belief relaxation are actually corrective with regard to dysfunctional beliefs. Following what has been said in the previous sections, this may in fact often be the case in psychedelic therapy: Enabled by operant conditioning of acceptance, relatively avoidance-free exposure to a multitude of greatly intensified private events should often produce experiences that strongly contradict negative expectancies. When the resulting large prediction errors impinge upon relaxed avoidance-related beliefs, they may exert a uniquely therapeutic corrective influence. Under favorable conditions, this could give rise to heavily-weighted and highly generalized *acceptance beliefs* (e.g. "Anxiety is not dangerous"). Apart from changes in explicit attitudes, belief relaxation may also facilitate the revision of more implicit expectancies, and reduce threat responses to private events through mechanisms related to extinction learning. In this respect, psychedelic therapy may resemble fear exposure treatment in CBT. Similar mechanisms have been proposed to underlie the therapeutic effects of mindfulness, which aims to broadly reduce reactivity to private events and is widely applied as a means of exposure in third-wave CBTs (25, 35–37). In line with the idea that psychedelic states can resemble the exposure-like quality of exercising mindfulness, psychedelics appear to enhance mindfulness capabilities (77–79), and mindfulness-related practices can enhance positive effects of psychedelics (80). It is well established that extinction learning in exposure treatments is most effective when negative expectancies regarding the outcomes of exposure are maximally violated (33). Psychedelic therapy appears to provide favorable conditions in this regard: First, the intense and often disturbing nature of the psychedelic experience may induce particularly negative expectancies about the outcomes of desisting from avoidance (e.g., "If I stop trying to control it, the anxiety will become absolutely unbearable"). By contrast, actual outcomes of avoidance-free exposure will often comprise a sense of breakthrough that is experienced as strongly rewarding, thus strongly violating negative expectancies. Following the relaxed-beliefs account, the effects of such expectancy violation on extinction learning should be further amplified by psychedelic-induced increases in sensitivity to prediction errors.

To summarize, psychedelic experiences that involve breakthrough experiences and episodes of relatively avoidance-free exposure to otherwise avoided private events may constitute unique learning conditions where relaxed avoidance-related beliefs can be revised with beneficial results. Corresponding changes in explicit attitudes, preconscious assumptions, and more implicit expectancies may profoundly transform the patient's way of relating to private events. The following patient report illustrates how these changes may lead to long-term increases in acceptance:

> *I took away from the experience that I used to get angry about having anxiety, now I think I can have the anxiety, I can just feel it and it will go, I don't have to have the fear or run away.*
>
> Patient #2 (13)

IMPLICATIONS FOR RESEARCH

Measuring Acceptance-Related Processes in Psychedelic Therapy

The proposed conceptual model (**Figure 2**) can be understood as a specific formulation of the more generic extra-pharmacological (EP) model of psychedelic drug action by Carhart-Harris and Nutt (44). At its core, the EP model assumes that long-term responses to psychedelics are predicted by relevant aspects of the acute drug response (which, in turn, results from interactions between drug-related, personal, and environmental factors). Applied to our model, long-term increases in acceptance and corresponding reductions in psychopathology should be especially pronounced following psychedelic experiences where operant processes engender episodes of relatively avoidance-free exposure to otherwise avoided private events, thereby enabling the revision of avoidance-related beliefs. Whereas qualitative analyses of patient interviews (13, 48, 49, 51) are compatible with this view, quantitative studies are needed to test and further develop the proposed model. This requires that relevant aspects of the acute psychedelic experience are adequately measured. To this end, we are currently developing a new questionnaire with separate scales for measuring the proposed acceptance-related processes in psychedelic states. To further clarify the role of acceptance as an underlying mechanism of change in psychedelic therapy, baseline and follow-up assessments in future clinical studies should include instruments for measuring experiential avoidance [e.g., (57, 81)] and related phenomena such as avoidant coping [e.g., (82)], thought suppression (83), and beliefs about the unacceptability of emotions (84). Assuming that acceptance is a central factor in psychedelic therapy, one should expect positive clinical outcomes such as symptom reductions to be at least partially mediated by decreases in experiential avoidance. Furthermore, research into the predictability of treatment outcomes based on pre-treatment avoidance levels could be an important basis for future clinical decisions (see our discussion of clinical targets below).

Examining the Role of Challenging and Breakthrough Experiences

Challenging psychedelic experiences are potential starting points for acceptance-promoting learning processes, but are probably not always therapeutically valuable. In line with this, previous studies have found mixed results regarding long-term effects of challenging experiences: Roseman et al. (46) found that levels of anxiety and impaired cognition during psilocybin sessions predicted less positive clinical outcomes in depression patients. Likewise, a prospective survey study in a non-clinical sample (85) found that challenging psychedelic experiences had negative effects on subsequent well-being. Another survey (53) revealed that well-being was negatively related to the duration of challenging experiences, but positively related to their intensity. These seemingly contradictory results have been interpreted in the sense that "challenging experiences can indeed be

therapeutically beneficial, but only if personal insight and/or emotional catharsis follows the relevant experience(s) of psychological struggle" (64). The same authors have recently developed a questionnaire for measuring this breakthrough quality of challenging experiences, and observed that emotional breakthrough predicted increases in well-being after naturalistic psychedelic use (54). We acknowledge that the intense relief inherent in such experiences may act as a massive reinforcement of acceptance. However, according to our tentative model, the therapeutic value of breakthrough experiences may lie not only in breakthrough itself but also in the preceding shaping of acceptance, subsequent exposure to otherwise avoided private events, and corresponding changes in avoidance-related beliefs. This distinction may be irrelevant in many cases, but it could be important in situations where the patient undergoes episodes of relatively avoidance-free exposure without previously having a challenging experience (and thus perhaps without experiencing a sense of breakthrough). This relates to the important question how the acute psychedelic experience and clinical outcomes are affected by a repetition of active dosing sessions. Modern clinical trials have involved between one and three active dosing sessions, but to date, no comparative studies have directly investigated the effects of repeated dosing on acute and long-term outcomes. From the learning perspective presented here, challenging experiences in a second or third dosing session might be reduced to the degree that previous sessions involved the revision of avoidance-related beliefs. However, the patient may still—or even more than in previous sessions—undergo episodes of therapeutically valuable exposure. Hence, to differentiate between the interrelated but distinct aspects of the proposed acceptance-promoting learning process, it should be attempted to assess these aspects separately and across repeated dosing sessions.

Examining the Role of Ego-Dissolution Experiences

To date, most of the evidence supporting the EP model's core assumption that acute responses to psychedelics predict longer-term outcomes (44) relates to acute *ego-dissolution*, i.e., a transiently compromised experience of self that is characterized by a sense of unity with one's surroundings (86). From a predictive processing perspective, ego dissolution can be explained in terms of a transient disruption of self-related high-level beliefs (14, 87, 88). Blissful ego-dissolution and related phenomena such as "oceanic boundlessness" and "mystical-type experiences" have been shown to predict not only long-term increases in well-being (80, 85) and trait openness in non-clinical samples (59, 60, 89) but also positive clinical outcomes (5, 7, 11, 46). We propose the following interpretation of these findings: As discussed above, the patient may engage in overt avoidance behaviors (e.g., removing eyeshades or moving around) to reduce the intensity of acute drug effects, thereby reducing the likelihood of ego-dissolution. Likewise, covert (internal) avoidance strategies that involve self-referential processing (e.g., worrying) may to some extent impede the disruption of self-related high-level beliefs. By implication, ego-dissolution phenomena are less likely to occur when personal or contextual factors hinder acceptance-promoting learning processes such as that outlined in our conceptual model. Hence, the occurrence of mystical-type experiences or oceanic boundlessness can be seen as a (massively rewarding) consequence of having learned to let go of avoidance strategies [see (90) for recent evidence supporting this view]. The observation that blissful ego-dissolution is followed by long-term reductions in psychopathology, greater well-being, and increased openness may thus, at least in part, be explained in terms of reduced avoidance. In line with this idea, a recent survey study (91) found that the impact of acute mystical-type effects on decreases in depression and anxiety after naturalistic psychedelic use was entirely mediated by increases in psychological flexibility (a construct that is closely related to acceptance). Some positive effects of ego-dissolution could nonetheless be relatively unrelated to acceptance [e.g., see (92)]. To further investigate the therapeutic role of ego-dissolution experiences, future clinical studies should complement measures of ego-dissolution with measures of acceptance-related processes in the psychedelic state.

CLINICAL CONSIDERATIONS

Integrating Psychedelic Interventions Within Cognitive-Behavioral Treatment Models

According to the proposed model (**Figure 2**), psychedelics can facilitate the same acceptance-promoting learning process as that targeted by CBT interventions. This suggests that there are large potential synergies between CBT and psychedelic therapy. In line with this, it has been proposed that psychedelics could be fruitfully integrated within acceptance-based CBTs, most notably ACT [(13, 42, 93–96); for recent ACT-based protocols for psilocybin-assisted treatment of depression see (97, 98)]. We agree with this view, but emphasize that the proposed model is suited as a theoretical framework for integrating psychedelic therapy with not only ACT and other acceptance-based approaches but CBT more generally[4]. After all, all cognitive-behavioral treatment models seek to help patients find more adaptive (less avoidant) ways of relating to private events. Apparent disparities between third-wave and second-wave CBT models may be more accurately described as differences in viewing angles and preferred therapeutic techniques than differences in targeted psychological processes (99): Just as acceptance techniques used in ACT can be understood as methods for challenging avoidance-related beliefs, cognitive restructuring techniques in traditional CBT can be seen as ways of encouraging acceptance (100). From this perspective, it appears that limiting the integration between psychedelic therapy and CBT to techniques belonging to one or the other CBT model would unnecessarily narrow down the repertoire of available interventions. Hence, we propose an empirical approach to the question of which particular CBT interventions are

[4]Beyond CBT, most other schools of psychotherapy also recognize the role of experiential avoidance or related concepts in human suffering (21). Therefore, although our model is formulated in CBT terms, it may still add a valuable perspective to how proponents of other schools (e.g., psychodynamic therapy) understand the therapeutic value of psychedelic states.

best suited to amplify the acceptance-promoting effects of psychedelic therapy: Future clinical studies with psychedelics should investigate how effect sizes are affected by systematically varying psychological interventions, and assess whether these effects are moderated by patient characteristics. Such variations should not be restricted to preparatory and integration sessions, but may also involve gentle deviations from the prevailing traditional non-directive approach for dosing sessions (e.g., therapists actively addressing avoidance-related beliefs).

Whenever considering acceptance as a mechanism of positive change, it is important to note that acceptance should not be seen as an end in itself, but rather as a requirement for living in accordance with one's chosen values (38, 100). The reciprocal relationship between acceptance and values may be reflected in the observation that patients commonly report reconnecting with personal values or discovering new ones through the psychedelic experience (13, 48, 101, 102). On this basis, it can be assumed that treatment outcomes could be optimized by including values work in treatment. Psychedelic therapy protocols that involve values-based interventions have been described [e.g., (97, 103)]. To further improve treatment models, the impact of such interventions on treatment outcomes should be investigated systematically.

Direct Implications of the Model for Clinical Practice

A central hypothesis presented here is that psychedelics can transiently compromise the effectiveness of avoidance strategies for (in the very short run) reducing aversive states. This may constitute a major difference between psychedelic therapy and more conventional methods in psychotherapy (where the patient can more easily reduce aversion by resorting to avoidance), and has important ethical implications for clinical practice. Most importantly, for the patient to be able to provide informed consent, they should be thoroughly informed about potential avoidance-impeding effects of the treatment. This requires that patients are given the opportunity to learn what avoidance is, and may involve not only educational but also experiential elements. Hence, the process of enabling valid informed consent for psychedelic interventions may already necessarily involve substantial elements of psychotherapy.

According to our model, operant conditioning of acceptance requires the patient to "start the ball rolling" by spontaneously showing a minimum of acceptance toward an aversive aspect of the experience at some point. Apart from the obvious implications that are already accommodated by current protocols for preparatory sessions (e.g., building an atmosphere of safety and trust; training mindfulness; setting intentions for acceptance), this may inform therapeutic strategies for dealing with challenging experiences: Whereas therapists may initially attempt to facilitate breakthrough by encouraging acceptance, challenging experiences that persist for longer periods of time may indicate that the patient cannot (at present) desist from avoidance sufficiently to induce shaping of acceptance. This situation entails the risk that motivation for acceptance is markedly decreased and further attempts are impeded. It may therefore in some situations be therapeutically beneficial to actually support the patient's decision for avoidant responding before encouraging acceptance again. The ability to gauge the individual patient's distress tolerance on a moment-to-moment basis and strike a sensible balance between encouraging acceptance and supporting avoidance can be considered a key requirement for psychedelic therapists, and should be trained accordingly. It can be argued that such perspective-taking requires first-hand experience with psychedelic states [see (104) for a discussion of this matter].

The proposed model explains increases in acceptance after psychedelic therapy in terms of revised avoidance-related beliefs. After the dosing session, newly established acceptance beliefs and corresponding behavior change may be more or less enduring depending on how generalized and heavily-weighted those beliefs are. In any case, long-term outcomes should be substantially affected by the learning conditions that the patient is exposed to after acute drug effects subside. In most cases, the patient will soon return to an environment that has been to some extent organized around avoidance goals. Continued psychotherapy may then help identify and change persistent habits, routines, and other circumstances that impede the pursuit of more acceptance-oriented approach goals. The same applies to individual deficits that hinder the abandonment of avoidant coping strategies (e.g., deficient social competencies or problem-solving abilities). Therapists should also pay attention to how the patient's social environment responds to changes in behavior and attitudes. For instance, returning to an emotionally invalidating or dismissive environment without appropriate therapeutic support may result in rapid re-establishment of pathological avoidance-related beliefs. It appears unlikely that two or three integration sessions suffice to address such challenges in all cases. Hence, the prevailing brief intervention models employed in contemporary psychedelic therapy studies (42) may not adequately serve the needs of all patients, particularly those with limited personal or social resources.

Clinical Targets

Assuming that promoting acceptance is one of its core mechanisms, psychedelic therapy can be expected to have most pronounced positive effects in those mental disorders that are typically characterized by excessive experiential avoidance. This encompasses many of the most prevalent mental disorders, including some that are already in the focus of psychedelic research (e.g., depression and addiction) and others for which modern clinical trials have not yet been conducted, such as panic disorder, posttraumatic stress disorder (PTSD), or psychosomatic disorders. Psychedelic therapy may hold less promise for conditions where avoidance is not considered a central factor, such as attention-deficit/hyperactivity disorder (ADHD) or psychotic disorders (15). Especially in the latter patient group, this may shift the risk-benefit ratio against psychedelic interventions. In line with this, pre-prohibition clinical studies, which tested psychedelics for mental disorders across the board, found positive results mostly in (then so-called) "psychoneurotic" disorders (105).

Within suitable diagnostic categories such as depression or addiction, how to determine if an individual patient is likely to benefit from acceptance-informed psychedelic therapy? On the one hand, it can be speculated that those patients who exhibit

particularly high levels of experiential avoidance at baseline have the greatest potential for improvement. On the other hand, there may be a tipping point at which patterns of avoidance are too inflexible to make use of challenging psychedelic experiences. According to the proposed model, the shaping-like operant process of conditioning acceptance can be initiated only when the patient is able to show a minimum of acceptance spontaneously. If this is impossible due to personal (or contextual) factors, this may give rise to prolonged challenging experiences that have no therapeutic value or could even aggravate avoidance-related beliefs. One might assume that such tipping points are localized around the threshold where the inflexibility and pervasiveness of experiential avoidance and related patterns of emotion dysregulation justify the diagnosis of a personality disorder (e.g., avoidant personality disorder or borderline personality disorder). However, excluding patient populations based on such ideas seems premature without empirical support, especially when considering the substantial need to improve current treatments for personality disorders. Zeifman and Wagner (96) made a strong case for exploring the incorporation of psychedelics within interventions for borderline personality disorder (e.g., DBT), basing their argument partly on these substances' acceptance-promoting effects. Further research into the predictability of acute and long-term responses to psychedelics is needed to determine criteria for psychedelic treatment eligibility. While it is common practice in clinical trials to exclude patients based on rather trait-like attributes (e.g. diagnosis of a personality disorder), state measures (e.g. quality of the therapeutic relationship or clarity of acceptance-oriented intentions) may eventually emerge as more robust (and perhaps mediating) predictors of treatment outcomes.

Applicability to MDMA-Assisted Psychotherapy

Although not a classic psychedelic, the entactogen 3, 4-methylenedioxymethamphetamine (MDMA) is applied in therapeutic interventions following protocols which closely resemble those used for psychedelic therapy (106). For some patients who are unsuited (or unwilling) to undergo treatment with classic psychedelics, MDMA may be considered as a more easily tolerable alternative (106). MDMA-assisted psychotherapy shows remarkable promise as a treatment for PTSD (107), and appears to work by facilitating engagement with traumatic memories and supporting fear extinction (108). Thus, as is proposed here for (classic-)psychedelic therapy, MDMA-assisted psychotherapy may parallel CBT in promoting motivation for acceptance, avoidance-free exposure, and the revision of avoidance-related beliefs. However, the mechanisms underlying these processes are likely different for MDMA and classic psychedelics given their distinct psychopharmacological action. Many of these differences, which cannot be discussed at length here, are potentially relevant for clinical decisions. Perhaps most importantly whereas we propose that classic psychedelics increase motivation for acceptance *via* avoidance sensitivity (making avoidance more aversive), MDMA seems to facilitate engagement with otherwise avoided private events primarily by attenuating the fear response (making acceptance less aversive). Clinical applications of MDMA-assisted psychotherapy are currently being extended beyond PTSD (106), and PTSD may become a target of treatments with classic psychedelics in the future (109). Hence, commonalities and differences in the psychological mechanisms underlying MDMA- and (classic-)psychedelic-assisted therapies may become important considerations in future clinical decision making, and should be investigated accordingly.

CONCLUSION

The therapeutic effects of psychedelics appear to depend on psychological processes that are evoked by synergies between these substances' pharmacological action and the context in which they are administered. To better understand and further develop psychedelic therapy, theoretical models that specify these processes are needed. Here, we took a CBT perspective and proposed such a model based on Carhart-Harris and Friston's (14) relaxed-beliefs account of psychedelics' acute brain action: When combined with specific context factors that are typically present in psychedelic therapy, belief relaxation can increase motivation for acceptance *via* operant conditioning, thus engendering episodes of relatively avoidance-free exposure to greatly intensified private events. Under these unique learning conditions, relaxed avoidance-related beliefs can be exposed to corrective experiences and become revised accordingly, potentially leading to long-term increases in acceptance and associated reductions in psychopathology. This model shows substantial parallels between psychedelic therapy and CBT that may be harnessed by using CBT as a therapeutic framework for psychedelic interventions. Empirical research is needed to validate and further develop the proposed model and, more generally, to examine the relative importance of acceptance as a mechanism of action in psychedelic therapy. Therefore, appropriate instruments for measuring processes related to avoidance and acceptance in psychedelic states must be developed. Although still requiring further empirical support, the proposed model demonstrates the usefulness of the relaxed-beliefs account as a basis for building theories of the therapeutic effects of psychedelic drugs.

AUTHOR CONTRIBUTIONS

MW and HJ conceived the central theoretical ideas presented in this article. RE, LM, MK, FB, and GG provided critical feedback. The manuscript was written primarily by MW with contributions from RE, LM, MK, FB, GG, and HJ.

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REVIEW
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Depression, Mindfulness, and Psilocybin: Possible Complementary Effects of Mindfulness Meditation and Psilocybin in the Treatment of Depression. A Review

*Kristin Heuschkel and Kim P.C. Kuypers**

Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, Netherlands

Depression is a major public health problem that affects approximately 4.4% of the global population. Since conventional pharmacotherapies and psychotherapies are only partially effective, as demonstrated by the number of patients failing to achieve remission, alternative treatments are needed. Mindfulness meditation (MM) and psilocybin represent two promising novel treatments that might even have complementary therapeutic effects when combined. Since the current literature is limited to theoretical and empirical underpinnings of either treatment alone, the present review aimed to identify possible complementary effects that may be relevant to the treatment of depression. To that end, the individual effects of MM and psilocybin, and their underlying working mechanisms, were compared on a non-exhaustive selection of six prominent psychological and biological processes that are well known to show impairments in patients suffering from major depression disorder, that is mood, executive functioning, social skills, neuroplasticity, core neural networks, and neuroendocrine and neuroimmunological levels. Based on predefined search strings used in two online databases (PubMed and Google Scholar) 1129 articles were identified. After screening title and abstract for relevance related to the question, 82 articles were retained and 11 were added after reference list search, resulting in 93 articles included in the review. Findings show that MM and psilocybin exert similar effects on mood, social skills, and neuroplasticity; different effects were found on executive functioning, neural core networks, and neuroendocrine and neuroimmune system markers. Potential mechanisms of MM's effects are enhanced affective self-regulation through mental strategies, optimization of stress reactivity, and structural and functional adjustments of prefrontal and limbic areas; psilocybin's effects might be established *via* attenuation of cognitive associations through deep personal insights, cognitive disinhibition, and global neural network disintegration. It is suggested that, when used in combination, MM and psilocybin could exert complementary effects by potentiating or prolonging mutual positive effects, for example, MM potentially facilitating psilocybin-induced peak

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Stefan Borgwardt,
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***Correspondence:**
Kim P.C. Kuypers
k.kuypers@maastrichtuniversity.nl

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experiences. Future placebo-controlled double-blind randomized trials focusing on psilocybin-assisted mindfulness-based therapy will provide knowledge about whether the proposed combination of therapies maximizes their efficacy in the treatment of depression or depressive symptomatology.

Keywords: depression, mindfulness meditation, psilocybin, psychedelics, review

INTRODUCTION

Depression or major depressive disorder (MDD) is a common mood disorder and major cause of disability worldwide. Approximately 4.4% of the global population is affected by this condition, with wide-ranging variations across gender, age, and nationality (1). Typical symptoms include depressed mood, anhedonia, fatigue, feelings of worthlessness or guilt, changes in appetite, weight, and sleep, psychomotor retardation or agitation, executive deficits, and suicidal ideation (2). These are thought to originate from a complex interplay of psychological and biological factors (3).

Psychological factors that underlie the pathology of MDD comprise deficiencies on an emotional, cognitive, and social level (3). Negative thinking patterns paired with inadequate emotion regulation and excessive rumination have been implicated in the maintenance of depressed mood (4, 5). The aforementioned combination of these three psychological processes further promotes cognitive rigidity, as evident from underperformance in executive functioning tests measuring for example task-switching, working memory (WM), attention, and inhibitory control (4, 6–8). To exemplify, depressed patients take more time to adapt to new rules in the Wisconsin Card Sorting Test and show attentional and memory deficits predominantly in the context of positive affective stimuli (9, 10).

The emotional and cognitive deficiencies accompanying MDD have an impact on interpersonal competencies as well (11, 12). Not only do depressed people show differences in dispositional empathy compared to controls, with for example higher personal distress (13, 14), they also demonstrate shortcomings in communication skills, which might, for example, be expressed in an inanimate body language and bias toward negative facial expressions and conversational contents (12, 15). Additionally, they tend to seek excessively for approval and negative feedback, which may verify their negative self-image (12). Such poor social skills along with self-centered introversion provoke conflicts within the social environment, which pose stressors that crucially contribute to the perpetuation of depressive symptoms (16).

Biological factors that pertain to the characteristics of MDD range from neural imbalances to signaling dysregulations, partly grounded in genetic predispositions (3). Neuroplasticity, a crucial neural mechanism that entails structural and functional brain adaptations in response to altered environmental circumstances, is impaired in individuals with depression, as indicated by abnormally low levels of brain-derived neurotrophic factor (BDNF), the latter being related to hippocampal and prefrontal atrophy in MDD (17, 18). Deficiencies in MDD BDNF levels might originate from epigenetic factors, such as stress exposure (19, 20). A meta-analysis showed that clinical changes in depression were related to BDNF levels, and suggested a role for neuroplasticity in the improvement of symptoms (21)

Another biological disruption in MDD concerns the imbalances between functionally connected fronto-limbic and thalamo-cortical networks, which could further contribute to the maintenance of negative and rigid thinking patterns (22). More precisely, MDD is associated with hyper-connectivity within the default mode network (DMN), a system of brain areas engaged during rumination (22, 23). The DMN works in close accordance with the central executive network (CEN), a group of brain regions involved in WM and goal-directed behavior (24, 25), and the salience network (SN), which mediates the activity of the DMN and CEN according to the saliency of external or internal stimuli (26). In MDD, both the SN and CEN are intrinsically hypo-connected. In addition, the SN is generally hyper-connected to the DMN, while being over-responsive to negative emotional stimuli. This state relates to emotional over-reactivity in depressed patients. The CEN, on the other hand, is under-reactive to negative affective stimuli and its connections to the DMN and SN are weakened compared to that of healthy controls. This disrupted biological brain pattern is linked to deficits in executive functioning (27, 28).

MDD also features dysregulations within the hypothalamic-pituitary-adrenal (HPA) axis, a circuit within the neuroendocrine system that plays a central role in the regulation of stress and immune responses. Hypersecretion of cortisol and impaired negative feedback result in chronically elevated cortisol levels, which increase the vulnerability to stressors, cause disruptions in monoamine and immune systems, and ultimately promote the emergence of depressive symptoms (3, 18, 29). The inadequate HPA responsivity in MDD is further marked by a diminished cortisol awakening response (CAR), as opposed to healthy people who demonstrate steeply elevated cortisol levels within the first 30 min upon awakening (30, 31). Moreover, abnormally high levels of pro-inflammatory cytokines, such as interleukin 6 (IL-6), can be found in depressed patients (32), which is why theories link depression to inflammation (33). IL-6 has a stimulating effect on the HPA axis, and mediates BDNF levels (34, 35).

The outlined socio-cognitive and biological deficiencies can be categorized into six non-exhaustive broad factors, i.e., mood, executive functioning, social skills, neuroplasticity, neural core networks, and neuroendocrine and neuroimmunological factors. Although these factors seem to play a causal role in the symptomology of MDD to differing degrees, the precise etiology of depression is not known and cannot be delineated from the current evidence. The six individual factors presented

here appear to influence each other in a circular, perpetuating manner, as illustrated in **Figure 1**. Thus, the modulation of one factor is expected to exert a net effect across other factors, and subsequently to affect the overall depressive symptomology. Of note, there are more psychological (e.g., cognitive biases) and biological factors (e.g., serotonin transporter genotype) that are known to be involved in depression (36, 37); this review is limited to the six selected factors.

The sum of deficits within these factors has been shown to result in profound impairments in daily functioning (38), a reduced quality of life (38, 39), an increased risk of suicide (40), and a substantial lack of productivity (41, 42). This also renders MDD costly on an economical level. Estimates of the financial burden that can be ascribed to occupational incapacity due to depression approximate 33 billion euro per year in the United States of America alone, excluding treatment costs (43). Taken together it is clear that there is a pressing need to come up with alternative treatments for depression, next to the conventional first-line psycho- and pharmaco-therapies.

Conventional Treatments of Depression

A wide array of biological ("pharmacotherapy") and psychological ("psychotherapy") treatment options for depression is currently available, targeting different elements that are thought to be the underlying pathological cause in their specific theoretical framework (3). Common pharmacotherapy is predominantly based on the hypothesis that depression is caused by a deficiency of monoamine neurotransmitters, such as serotonin (5-HT), dopamine, and norepinephrine, and their receptors, which play an important role in the regulation of mood, arousal, and memory. By elevating these neurotransmitter levels to varying degrees, different types of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or monoamine-oxidase inhibitors, are assumed to reduce depressive symptoms (44). However, while being only partially effective in severe cases of depression, antidepressants (45) may also cause severe adverse effects, such as sexual dysfunction or cardiovascular risks (46, 47). Moreover, upon discontinuation, relapse rates are high, which is why antidepressants are often taken chronically (48).

Psychotherapy includes cognitive-behavioral therapy (CBT) and interpersonal therapy, both based on different psychosocial theories, focused on modifying, respectively, behavioral and cognitive biases by means of repeated counseling sessions with a therapist (3). Despite large effects in reducing depressive symptoms (49), relapse and drop-out rates are considerably high (50, 51). For this reason, common pharmaco- and psychotherapies for MDD are frequently combined, which has been acknowledged to be more effective than either approach alone (52). Nevertheless, a substantial proportion of MDD patients that fails to achieve full recovery remains, with almost 75% after 8 weeks and approximately a quarter after 24 weeks of treatment (53).

Alternative Treatments of Depression

In response to the profound limitations of conventional treatments of depression, several alternatives have been proposed (e.g., 54–56). Among these, two approaches that originate from spiritual practice traditions of indigenous and religious communities, namely mindfulness meditation (MM) and administration of classical psychedelics, have gained scientific interest in depression research (57, 58). With regard to the latter, a limited number of clinical trials have been conducted in depressed patients who were administered ayahuasca and psilocybin (59). Although these studies give preliminary evidence of their potential in the treatment of depression, caution regarding efficacy conclusions in depression is warranted due to the currently limited number of studies and small sample sizes (60–63).

For this review we have chosen to focus on psilocybin given the known safety profile in individuals (64) and the potential future of psilocybin therapy since it has received the "breakthrough therapy for treatment-resistant depression (TRD)" designation from the FDA (October 2018). The latter means that the FDA acknowledges that "there is preliminary clinical evidence that indicates that the drug may demonstrate substantial improvement over existing therapies on one or more

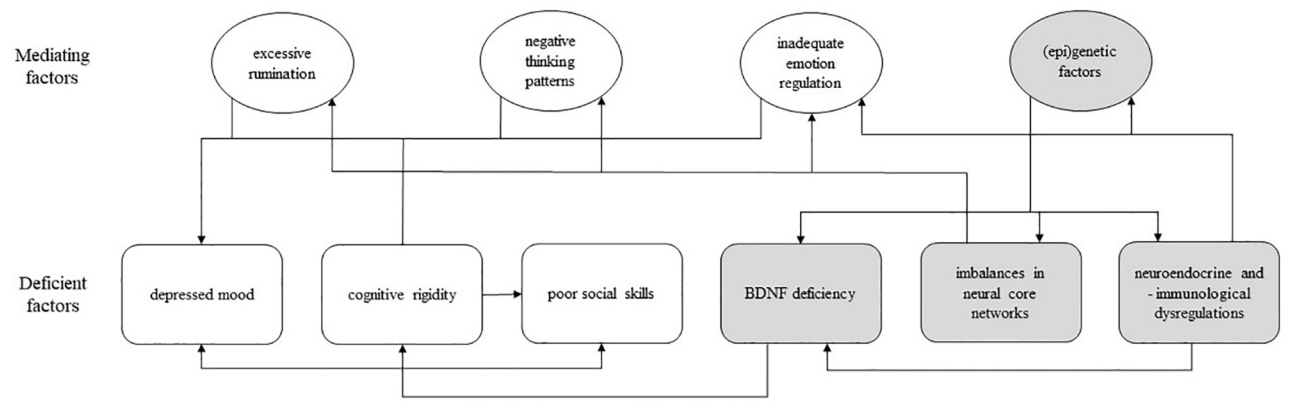

FIGURE 1 | A model of psychological and biological deficiencies associated with major depressive disorder; rounded square-shaped box, deficient factor(s); oval-shaped box, mediating factor(s); white box, psychological factor; gray box, biological factor; arrow, unidirectional influence; BDNF, brain-derived neurotrophic factor.

clinically significant endpoints, such as substantial treatment effects observed early in clinical development and that it will be used to treat a serious or life threatening disease or condition" (65).

MM and psilocybin are thought to exert their effects on behavior *via* a variety of psychological and biological mechanisms, potentially resulting in expeditious and long-lasting effects (e.g., 66–69).

Mindfulness Meditation

MM is a form of meditation derived from the Pali word "sati" that emphasizes the mental practice of present moment awareness in a non-judgemental and emotionally accepting fashion while remaining in a relaxed state (70, 71). In healthy populations, protracted MM practice (of several months) is linked to improvements in self-regulation and subjective well-being (72, 73). Of note, also shorter MM training (of e.g., four days) already has a positive impact on mood and executive functioning, while reducing fatigue and anxiety (74).

Different forms of MM may be applied, depending on the meditator's expertise and personal goals. Focused-attention meditation (FAM) involves the direction of attention towards a focal object and gentle reinstatement of this focus when thoughts drift off or strong emotions surface (75). This variant is usually employed by novice meditators. Open-monitoring meditation (OMM) involves no focal object, but rather non-selective awareness of the present moment, and is preferably operationalized among more advanced meditators. Loving-kindness meditation (LKM), on the other hand, combines technical components of FAM and OMM, and puts strong emphasis on the fostering of compassion and positive emotions (76, 77).

MM can be used as a supplement in psychotherapy, constituting mindfulness-based interventions (MBIs), of which mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) are the most common (78). These usually entail sessions guided by a professional in addition to at-home practice over a duration of eight weeks (78). MBSR specifically targets the management of stressful situations and is recommended as a supportive means in chronic diseases, whereas MBCT teaches strategies for dealing with maladaptive thought patterns, which makes it more suitable for the prevention of depressive relapse (60, 79).

Not only have MBIs demonstrated efficacy in the treatment of depression (61), but they are also effective in reducing symptoms in a variety of other psychiatric and medical conditions, such as social anxiety, drug-resistant epilepsy, and mental fatigue following brain damage (80–82). Due to its particularly enduring effects, MM is frequently incorporated as an adjunct in maintenance treatments for the prevention of relapse of depressive symptoms (83, 84) or utilized as alternative treatment in treatment-resistant patients (61). However, effect sizes of MBIs are only moderate (85), and, in order to fully benefit from mindfulness training, a certain meditation depth is required, which depends on individual predispositions and practice frequency (86).

Psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), on the other hand, is a classical tryptamine hallucinogen that can be derived from a variety of Psilocybe mushroom species (87). Upon oral administration, subjective effects become apparent after approximately 30 to 60 min, peak 90 to 180 min later and last up to 6 h in total (88). These effects are highly dose-dependent (89) and entail perceptual, cognitive, and emotional alterations, which may resemble the features of psychosis (90).

As psilocybin is metabolized into psilocin (4-hydroxy-N,N-dimethyltryptamine) upon ingestion, it is regarded as a prodrug (87, 91). Psilocin acts as a 5-HT agonist and has a particularly high affinity for the 5-HT2A receptor subtype, which is thought to be responsible for its psychotropic effects (92). An analysis by Johnson et al. (64) shows that, although psilocybin has some level of abuse potential and risk, there is no strong evidence of physical dependence, and it can in general be safely used under medical supervision. Nonetheless, adverse effects, such as anxiety or psychotic reactions, may occur when psilocybin is administered in an environment that could evoke negative emotions, as the drug tends to amplify the present affective state (93). Thus, the provision of psychological support and surroundings that are perceived as comfortable and safe are essential when applying psilocybin or other psychedelics in empirical or clinical trials (94).

If these precautions are taken, psilocybin suggests to promote long-lasting positive changes in well-being, attitude, and personality upon a single administration (88, 95). Apart from its potential therapeutic value in depression (63, 96, 97), psilocybin also holds promise for a variety of other conditions, such as anxiety in terminal illness, obsessive–compulsive disorder, and substance dependence (98–100). However, this evidence is still largely based on a limited number of small-scale controlled studies and hence preliminary, impeding its approval for clinical practice.

AIM AND OUTLINE

Due to its intrinsically mental and observant nature, MM can be seen as a psychologically focused approach; it is a specific way of paying attention, with a focus on being in the present, in a non-judgemental way. Similar to other trainings or exercises, MM has effects on neurobiological processes (101). Psilocybin is a pharmacological agent, acutely affecting neurobiological processes and inducing psychological effects. Both MM and psilocybin induce structural—longer-lasting—psychological and biological changes, and they show potential of being valuable novel alternatives in the treatment of depression.

In clinical psychedelic patient trials, psilocybin is always administered in a supportive setting, and followed by multiple integration sessions after the experience. Here, the inclusion of MM in the psychedelic-assisted psychotherapy might yield larger or longer positive effects than either treatment on its own, similar to the conjunction of conventional pharmacotherapy and psychotherapy (52).

Noteworthy here is that meditative elements, such as inward-directed attention and relaxation practices, are already being incorporated in psilocybin-assisted trials (69, 102, 103). One study in healthy volunteers concluded that determinants of the longer-lasting positive effects on prosocial attitudes and behaviors as well as psychological functioning following psilocybin administration were the psilocybin-occasioned mystical-type experience and the rate of meditative or spiritual practices (69). While very interesting and relevant in light of current developments psychedelic research, lacking here is a firm theoretical ground of such implications, as none of those studies has directly tested potential applications of a combination of both MM and psilocybin in the treatment of depression (69, 104).

Therefore, the present review aims to compare acute and long-term effects of MM and psilocybin on psychological and biological factors associated with depression in order to provide a theoretical understanding of the potential benefit when used in combination in the treatment of MDD. In each section, findings on the effects of MM and psilocybin will be presented with respect to the aforementioned six factors as depicted in **Figure 1**, followed by inferences about the potential beneficial effects when using them in combination.

The effects of MM and psilocybin are considered additive or complementary when their comparison suggests they both exert positive effects on the same factor, and when a theoretical combination is reasonably likely to yield superior effects over either treatment individually, with regard to effect duration (i.e., acute versus long-term effect), and/or underlying working mechanism (e.g., bottom-up versus top-down effect).

METHODS

In order to gain information on the individual effects and underlying working mechanisms of MM and psilocybin on the six selected MDD-related factors (three psychological, three biological), empirical articles, textbooks, and review papers were searched between September 2018 and January 2019, using the databases PubMed and Google Scholar. Three separate search strings were employed for "depression," "mindfulness meditation," and "psilocybin," which were, combined with the Boolean command "OR."

The search string for "depression" included terms related to the six factors proposed in the introduction (i.e., depression, mood, cognitive, social, interpersonal, neuroplasticity, BDNF, network, HPA axis, cortisol, stress, inflammation). The search string for "mindfulness meditation" included MM-associated concepts and interventions (i.e., mindfulness, meditation, mindfulness-based intervention, mindfulness-based cognitive therapy, mindfulness-based stress reduction). Although the focus of the review was on psilocybin, the search string for "psilocybin" also contained other classical psychedelics, as similar mechanisms of action may allow for inferences about psilocybin's potential effects (i.e., psilocybin, psilocin, psilocybin-assisted therapy, tryptamine, LSD, ayahuasca, DMT, 5-HT2A, psychedelic, hallucinogen).

An article was included when its focus was on psilocybin (or a classical psychedelic) and/or mindfulness, and comprised information relevant to the treatment of MDD. In addition, reference lists of included articles were searched. The literature search yielded a total of 1129 hits, of which 1047 publications were excluded since they did not match the inclusion criteria based on their title or abstract. The remaining 82 articles were individually analyzed and assigned to one or more of the six factors associated with depression; 13 articles were added after reference search lists of the included articles. In total, 95 articles were used for the present review (**Figure 2**). Among those, 67 were papers describing original ("experimental") research, seven were original research articles without an experimental manipulation (correlational), three were pooled data analyses, 12 were review papers, and the remaining six included theoretical (3) or editorial (1) pieces and one book. A summary of the papers describing original research is presented in **Table 1**.

PSYCHOLOGICAL FACTORS

As put forward in the *Introduction*, the psychological deficiencies of MDD feature a rigid, negatively biased cognitive style that contributes to the recurrence of depressed mood, regulatory difficulties, and social conflict (4, 7, 16). Below, studies describing the effects of MM and psilocybin on mood, executive functioning, and social skills are summarized.

Mood

MM has been found to elevate mood in healthy participants (74, 108, 168), depressed patients (131, 167) and other conditions (114, 161). For MBSR, this effect was already apparent after training units as short as three days (168) and remained up to six months (114), while MBCT demonstrated sustained effects for three months (161). Studies of mindfulness training that was not combined with psychotherapy only demonstrated short-term mood enhancement in healthy volunteers (74, 108).

It has been proposed that such mood enhancement arises from the acquisition of mental strategies. Mindfulness-based mental strategies are thought to reduce cognitive reactivity, the tendency to engage in negative thinking in response to mildly dysphoric mood, and promotes emotion acceptance, ultimately improving affect regulation (133, 154, 167, 169). Additionally, Huffziger and Kuehner (131) showed that by encouraging non-judgemental awareness of negative thoughts in depressed patients, the association between negative thoughts and negative mood might diminish, and the perpetuation or relapse of depressive symptoms prevented (131). This is in line with the negative association between mindfulness and rumination, and the positive relationship between mindfulness and nonattachment found in healthy volunteers. The latter indicates the degree to which an individual perceives happiness as independent from external circumstances, such as financial wealth or daily-life experiences (117). It is suggested that mindful individuals ruminate less and are consequently less likely to adapt their intrinsic state to affectively salient events in their environment (117, 131).

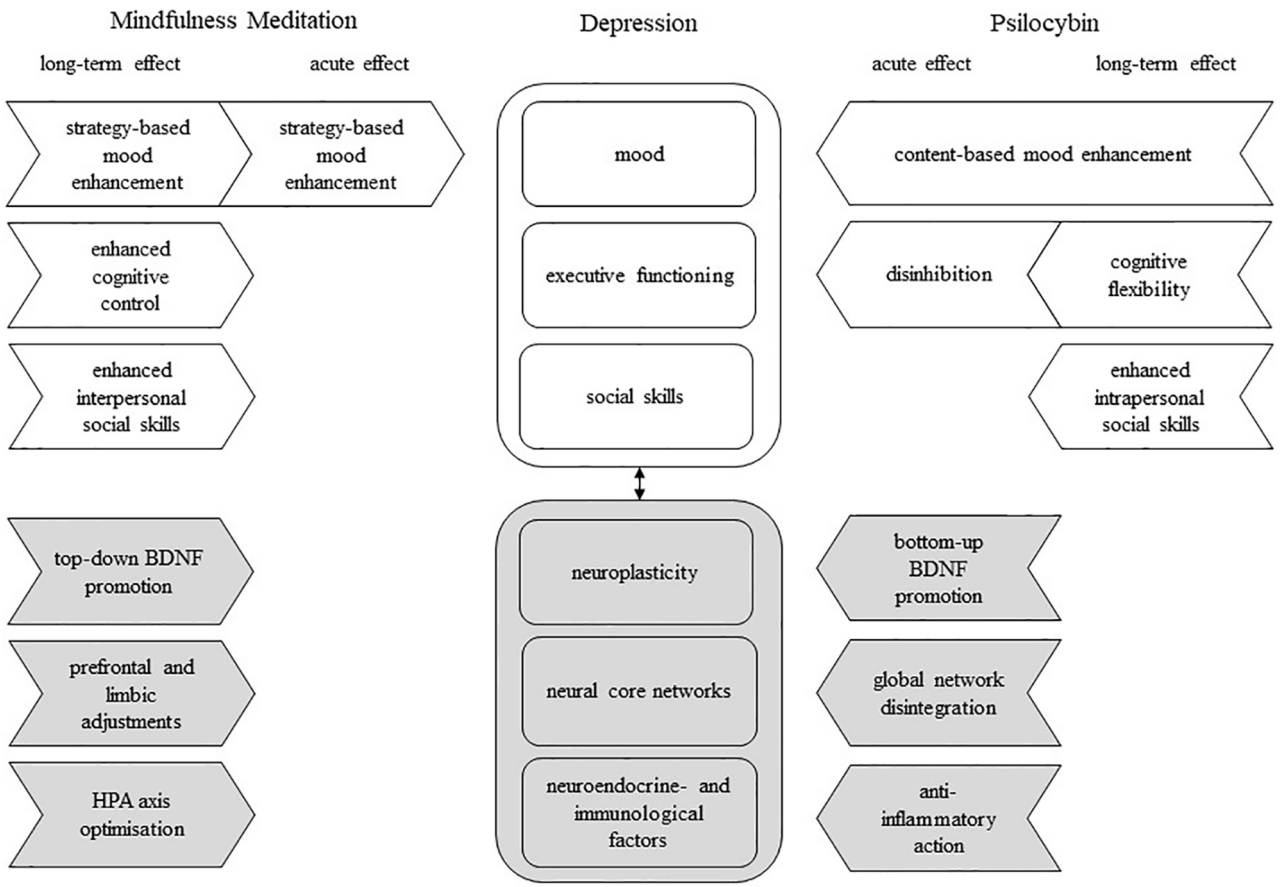

FIGURE 2 | A model of possible complementary effects of mindfulness meditation (MM) and psilocybin on psychological and biological deficiencies associated with major depressive disorder; rounded square-shaped box, deficient factor(s) in depression; arrow-shaped box, unidirectional effect; white box, psychological factor/effect; gray box, biological factor/effect; black arrow, interdependence; BDNF, brain-derived neurotrophic factor.

Psilocybin has been shown to acutely enhance mood in healthy participants (69, 96, 124, 134, 135, 151) as well as depressed (63, 103, 155) and cancer patients (96, 97, 99). This occurred after one to two fixed (10 and 25 mg, p.o.) or weight-adjusted doses (range between 1-30 mg/70 kg, p.o.), and in one study, the improvement was still significant at a 14-month follow-up with 0.2 mg/kg (14 mg/70 kg, p.o.) (99). Several lines of evidence further suggest that the mood-enhancing effect of psilocybin is dose-dependent (93, 88, 89, 128).

The acute effects of psilocybin occasionally involve a "peak" experience, a blissful sense of sacredness, revelation, transcendence of time and space, or connectedness with the environment (170). This often entails psycho-spiritual insights that are reported to be of major personal value and have an enduringly positive impact on well-being, attitude and personality (69, 97, 103, 124, 144). These persisting positive (mood) effects and relative freedom from worry is also called "afterglow" and indicated as an important timeframe for psychotherapeutic interventions (171, 172).

In summary, MM and psilocybin both induce positive mood changes which might outlast the acute MM or psilocybin stage. Effects of both seem to be "dose"-related with more extensive MM practice, and higher doses of psilocybin having more pronounced effects. Nonetheless, we suggest that MM and psilocybin have a different mechanism of action to induce the same effect. For MM, repeated training promotes the use of mental strategies, altering the cognitive frame in which negative thoughts are perceived and coped with (e.g., 133). With regard to psilocybin, perceptual and thought contents are directly altered by destabilizing established belief systems resulting in a restoration of adequate mood regulation (e.g., 69, 172, 173).

The combination of the strategy-based approach of MM with psilocybin's content-based approach (**Figure 2**) could possibly contribute to a potentiation or longer maintenance of induced mood enhancements. A reduction of cognitive reactivity and promotion of emotional acceptance through MM practice may prevent a relapse of negative thought patterns when the afterglow subsides. Also, Griffiths et al. (69) found that more extensive spiritual practice, including meditation, was associated with a higher frequency of psychedelic-induced peak experiences. This implies that MM practice might be able to facilitate peak experiences, which would result in an increased likelihood of

TABLE 1 | Overview of experimental studies and other types of studies (e.g., no intervention or pooled data analysis) included in the review; only constructs and findings (increase ↑/reduction ↓) related to the model are presented; *the most used abbreviations are BS, Between Subject; WS, Within Subject; MM, Mindfulness Meditation (or related); P, Psychedelic; Psi, Psilocybin; p.o., per oral; IV, intravenously; the other abbreviations are explained in the footnote of this table*.

Study	Sample (size)	Design/Intervention	Construct (measure)	Findings	MM/P
Astin (105)	Healthy participants (N=28)	BS, 2 groups: 8-weekBSR programme or non-intervention control condition	Psychological symptomology (SCL-90; perceived control; spiritual experience)	MBSR group > control group: ↓ overall psychological symptomatology, ↑ overall domain-specific sense of control, ↑ scores on a measure of spiritual experiences	MM
Alonso et al. (106)	Healthy male volunteers with prior experience with psychedelics (N=10)	WS, 2 sessions: placebo and freeze-dried ayahuasca (0.75 mg DMT/kg equivalent dose, p.o.)	Directed functional connectivity (transfer entropy)	Ayahuasca: ↓ top-down control (anterior regions), ↑ bottom-up (posterior regions) information transfer in the human brain	P
Barnes et al. (107)	Study 1: dating undergraduate students (N=89); Study 2: 30 heterosexual couples (N=60)	Study 1 (WS): short-term longitudinal measurement over 10 weeks; Study 2 (WS): Conflict discussion paradigm	Both studies: Mindfulness (MAAS); Relationship satisfaction (DAS; IMS); Self-control (SCS); Only study 2: Mood (POMS); communicative and affective functioning (SCID); changes in perception of the partner and relationship	Mindfulness: ↑ relationship satisfaction, ↑ capacities to respond constructively to relationship stress, ↓ emotional stress responses, positive pre- and post-conflict change in perception of the relationship, ↑communication quality	MM
Barrett et al. (93)	Healthy hallucinogen users (N=20)	Double-blind, WS, 5 sessions: Psi (10, 20, and 30 mg/70 kg, p.o.), DXM (400 mg/70 kg, p.o.) and placebo	Psychomotor performance (motor praxis task); Memory (word-encoding, recall, and recognition task; letter N-back task); Visual perception (PLOT)	Psi: ↓ psychomotor performance, WM, episodic memory, associative learning, visual perception; dose-dependent effects	P
Broderick (108)	Healthy undergraduate students (N=177)	BS; negative mood induction + rumination (group 1), distraction (group 2), or MM (group 3)	Affect (PANAS); Thought-listing	Negative affect: group 3 < group 1 and 2	MM
Brown et al. (109)	Healthy undergraduate students (N=44)	BS; Trier Social Stress Test or control task	Cortisol; Mindfulness (MAAS); Perceived stress (PSS), Anxiety (POMS); Negative affectivity (PANAS); Fear of negative evaluation (FNE)	Mindfulness: ↓ cortisol response to social stress, anxiety, negative affect	MM
Cahn et al. (110)	Healthy participants (N=38)	WS; 3-month yoga and meditation retreat	Psychometric measures (BSI, FMI, Tellegen Absorption Scale), serum BDNF levels; circadian salivary cortisol levels; pro- and anti-inflammatory cytokines	↓ Anxiety, depression, pro-inflammatory cytokine IL-12; ↑ mindfulness, BDNF, CAR), anti-inflammatory cytokine IL-10 plasma levels, other pro-inflammatory cytokines	MM
Barrett et al. (93)	Healthy participants, not drug naive (N=20)	Double-blind, WS, 5 sessions: Psi (10, 20, 30 mg/70 kg, p.o.), DXM (400 mg/70 kg, p.o.), and placebo	Subjective drug effects (Subjective Effects Questionnaire, Drug effect intensity rating, SOCQ, 5D-ASC, Mysticism Scale, Psychological Insight Questionnaire, Challenging Experience Questionnaire)	Psi (30 mg/kg) and DXM (400 mg/70 kg): similar profiles of subjective experiences ↓ psychomotor performance, balance; Psi > DXM: visual, mystical-type, insightful, and musical experiences; Psi < DXM: disembodiment, nausea/emesis, light-headedness	P
Carhart-Harris et al. (111)	Healthy participants with previous experience with a hallucinogenic drug (N=30)	WS, 2 sessions: Psi (2 mg in 10-mL saline) and placebo	CBF (fMRI); changes in venous oxygenation; intensity of subjective effects	Psi: ↓ CBF, which was maximal in hub regions (e.g. thalamus, ACC, PCC),↓ positive coupling between mPFC and PCC., ↓ ACC activity predicted the intensity of the subjective effects	P
Carhart-Harris et al. (112)	Healthy participants (N=15)	WS, 2 session: Psi (2 mg, IV + 10 mL saline) and placebo (10 mL saline)	Functional connectivity (fMRI)	Psi: ↑ functional connectivity between DMN and CEN, preserved thalamocortical connectivity	P
Carhart-Harris et al. (103)	Unipolar, treatment-resistant major depression patients (moderate-to-severe) (N=12)	Open-label, two doses of Psi (10 mg and 25 mg, p.o.) 7 days apart, supportive setting	Depressive symptoms (QIDS, BDI, HAM-D, MADRS, GAF), Anxiety (STAI), Anhedonia (SHAPS)	↓ Depressive symptoms, anxiety, anhedonia 1 week and 3 months after (25 mg) treatment compared to baseline	P
Carhart-Harris et al. (63)	Patients with moderate-to-severe, unipolar, treatment-resistant major depression (N=20)	Open-label, uncontrolled administration of Psi (10 mg and 25 mg, p.o. 7 days apart), supportive setting	Depressive symptoms (QIDS), BDI, HAM-D, MADRS, GAF), state-trait anxiety (STAI), anhedonia (SHAPS)	↓ Depressive symptoms until 6-month follow-up; response (n=9) was predicted by acute psychedelic experience quality; remitters (n=4)	P

(Continued)

TABLE 1 | Continued

Study	Sample (size)	Design/Intervention	Construct (measure)	Findings	MM/P
Carlson et al. (113)	Early stage breast and prostate cancer patients (N=42)	8-week MBSR programme	QOL (EORTC QLQ-C30); Mood (POMS), stress symptoms (SOSI); Salivary cortisol; Plasma DHEAS; Salivary melatonin	↑ QOL, associated with ↓ afternoon cortisol levels; ↑ sleep quality; ↓ symptoms of stress;	MM
Carlson et al. (114)	Cancer outpatients (N=54)	7-week MM programme	Mood (POMS); Stress symptoms (SOSI)	↓ Mood disturbance and stress until 6-month follow-up	MM
Carter et al. (115)	Healthy participants (N=8)	Double-blind, WS, 4 sessions: placebo, ketanserin (50 mg, p.o.), Psi (215 mg/kg, p.o.), and Psi + ketanserin	Attentional tracking ability (multiple-object tracking task); Spatial WM (spatial WM task)	Psi: ↓ attentional tracking ability (not attenuated by pre-treatment with ketanserin)	P
Carter et al. (116)	Healthy participants (N=10)	Double-blind, WS, 4 sessions: pre-treatment with ketanserin (50 mg, p.o.) or placebo, followed by administration of Psi (215 μg/kg, p.o.) or placebo	Subjective drug effects (AMRS, 5D-ASC), Binocular rivalry (binocular rivalry switch rate)	Psi: ↓ rate of binocular rivalry switching (not blocked by ketanserin); ↑ proportion of transitional/mixed percept experience; ketanserin: ↓ P's hallucinogenic symptoms	P
Coffey and Hartman (117)	2 independent, healthy undergraduate student samples (sample 1: n = 204; sample 2: n = 258)	Observational study; Structural equation modeling to test the mediation role of emotion regulation, nonattachment, and reduced rumination in in the relationship between mindfulness and a psychological distress factor	Mindfulness (MAAS); Emotion regulation (TMMS-Repair subscale); Nonattachment (Linking Inventory); Rumination (RRQ); Psychological distress (BSI)	Inverse relationship between mindfulness and psychological distress and emotion regulation, nonattachment, and rumination significantly mediated this relationship.	MM
Domínguez-Clavé et al. (118)	Volunteers (N= 45; of which 12 with borderline personality disorder (BPD) traits)	Naturalistic ayahuasca study; tests were administered prior to and 24 h after the ayahuasca session	Emotion regulation (DERS); mindfulness (FFMQ), Decentering (EQ); Borderline Personality Disorder (MSI-BPD)	Participants ↑ in mindfulness capacities and emotion regulation. The BPD-like subgroup ↑in emotion regulation; no changes in mindfulness capacities	P
Frecska et al. (119)	Participants of ayahuasca rituals (N= 40)	Naturalistic study; Assessments before and two days after the end of a two-week long ceremony	Visual creativity (Torrance Tests of Creative Thinking)	Highly original solutions and phosphenic responses ↑ number	P
Gex-Fabry et al. (120)	Patients remitted from recurrent depression (N = 56; MBCT: n = 28; TAU: n = 28)	BS: 8-week MBCT + TAU or TAU alone	Cortisol (CAR, average day exposure, diurnal slope); depression (MADRS, BDI); relapse (SCID)	Unchanged cortisol secretion patterns following participation in MBCT or TAU	MM
Gotink et al. (121)	Adult participants (previously completed MBSR or MBCT course) (N=29)	WS+BS: Mindful walking in nature for 1, 3, 6, or 10 days with a control period of a similar number a of days 1 week before the mindful walking period	Affect and state mindfulness (ESM); Depression, anxiety and stress (DASS-21); Mindfulness skills (Toronto Mindfulness Scale)	Mindful walking: ↑ mindfulness (predicted ↓ negative affect), positive affect, state mindfulness; positive affect and mindfulness prospectively enhanced each other in an upward spiral	MM
Greenberg et al. (122)	Study 1 (N=35): experienced mindfulness meditators (n=14) and non-meditators registered for their first meditation retreat (n=21); Study 2 (N=76): non-meditators	Study 1: BS; Study 2: BS, 8-meeting mindfulness programme or waiting list	Cognitive rigidity (Einstellung water jar task (Study 1 and 2)), Alphabet-Maze task (Study 2)	Rigidity scores experienced mindfulness meditators < non-meditators; rigidity scores non-meditators with mindfulness programme < waiting list group	MM
Greenberg et al. (123)	Non-meditators (N=76)	BS; 8-session mindfulness training programme or waiting list	Task set inhibition (BI, CRS)	Mindfulness programme: ↑ BI, but not CRS, compared to a waiting list group	MM
Griffiths et al. (88)	Healthy participants (N=18)	Double-blind, WS, 5 sessions: Psi (5, 10, 20, 30 mg/70 kg, p.o.) and placebo	acute subjective drug effects (HRS, APZ, 5D-ASC, Mysticism Scale, SOCQ, ARCI); retrospective persisting effects (PEQ); attitudes/dispositions/	Psi (20 and 30 mg/70 kg): mystical-type experiences that have persisting (1 and 14 months) positive effects (↑) on attitudes, mood, and behavior	P

(Continued)

TABLE 1 | Continued

Study	Sample (size)	Design/Intervention	Construct (measure)	Findings	MM/P
			behavior (Mysticism Scale, Death Transcendence Scale, Community Observer Ratings)		
Griffiths et al. (96)	Cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety (N=51)	Randomized, double-blind, WS: Psi (1 or 3 mg/70 kg, p.o.) and Psi (22 or 30 mg/70 kg, p.o.)	Depression (HAM-D, BDI, HADS); Anxiety (HAM-A, HADS, STAI, LAP); Mood (POMS); Self-rated psychiatric symptoms (BSI); Wellbeing (QOL); Optimism (LOT-R); Life meaningfulness (PILT); Understanding of self/others/life (LAP); Other-ratings of participant's mood/attitude/behavior	Psi (22 or 30 mg/70 kg): ↓ depressed mood, anxiety, ↑ QOL, life meaning, optimism, up until 6-months; participants attributed ↑ in attitudes to Psi (20 or 30 mg/70 kg) experience, consistent with other-ratings; mystical-type Psi experience on session day mediated the effect of Psi dose on therapeutic outcomes.	P
Griffiths et al. (69)	Healthy participants (N=75; 25 per condition)	BS; 6-8-month programme of meditation/ spiritual practices + double-blind administration of one of three doses of Psi p.o.: (1) 1 mg/70 kg + moderate-level support; (2) 20 and 30 mg/70 kg + moderate-level support; (3) 20 and 30 mg/70kg + high support	Persisting effects attitudes (Brief RCOPE, Gratitude Questionnaire, LAP, Trait Forgiveness Scale, Inclusion of Others in the Self scale, ASPIRES, Dispositional Positive Emotions Scale, LOT-R, SWLS, PILT, Other-ratings of participant's mood/ attitude/behavior	Psi: ↑ interpersonal closeness, gratitude, life meaning/ purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, community observer ratings at 6 months; Psi (20 and 30 mg/kg) > Psi 1 mg/kg; enduring effects depended on Psi-occasioned mystical-type experience and rates of meditation/spiritual practices	MM +P
Griffiths et al. (124)	Healthy adults who regularly participate in religious/ spiritual activities (N=36), hallucinogenic-naïve	WS, 2-3 sessions: Psi (30 mg/70 kg, p.o.) and methylphenidate (40 mg/70 kg, p.o.)	Affect (PANAS); Well-being (QOL); personality (NEO-PI); spirituality (Spiritual Transcendence Scale; Faith Maturity Scale; FACIT)	Psi: ↑ positive attitudes, mood, social effects and behavior at 2- and 14-month follow-up; Psi occasioned experiences similar to spontaneously occurring mystical experiences	P
Griffiths et al. (102)	Hallucinogen-naïve healthy adults who regularly participate in religious/ spiritual activities (N= 36)	WS, 2-3 sessions: Psi (30 mg/70 kg, p.o.) and methylphenidate (40 mg/70 kg, p.o.)	Affect (PANAS); Spirituality (Mysticism scale); Other-ratings of participant's mood/attitude/behavior	Psi: 2 months self- and other-rated sustained positive changes in attitudes and behavior	P
Grob et al. (99)	Adults with advanced-stage cancer, and anxiety (N=12)	Double-blind, WS, placebo-controlled, Psi (0.2 mg/kg, p.o.)	Depression (BDI); Mood (POMS); Anxiety (STAI); Psychiatric symptoms (BPRS)	Psi: ↓ anxiety, depressive symptoms at 1 and 3 months	P
Håkansson et al. (125)	Healthy older participants (N=19)	WS, 3 sessions: 35 min of physical exercise (condition 1), cognitive training (condition 2) or mindfulness practice (condition 3)	Neuroplasticity (serum BDNF levels)	Condition 1 > condition 2-3: ↑ serum BDNF levels	MM
Hargus et al. (126)	Depressed patients who had experienced suicidal crises (N=27)	BS; MBCT + TAU or TAU alone	Depression (SCID, BDI); meta-awareness (MACAM); specificity of memory (ReSSI)	MBCT > TAU: ↑ meta-awareness, specificity of memory	MM
Harman et al. (127)	Professionally employed males (N=27)	WS: mescaline (200 mg, p.o.)	Creativity (Purdue Creativity Test, Miller Object Visualization Test, Witkin Embedded Figures Test); Subjective ratings	↑ creative problem-solving for at least some weeks subsequent to the psychedelic session	P
Hasler et al. (128)	Healthy participants (N=8)	Double-blind, WS, 5 sessions: placebo, Psi (45, 115, 215 and 315 μg/kg, p.o.)	Attention (FAIR); Mood (AMRS), blood chemistry (plasma concentrations of thyroid-stimulating hormone, prolactin, cortisol, adrenocorticotropic hormone)	Psi: ↑ physiological parameters in a dose-dependent manner; Psi (215 & 315 μg/kg): ↓ attentional capacity	P
Hölzel et al. (129)	Healthy participants (N=26)	WS; 8-week MBSR programme	Perceived stress (PSS); amygdala grey matter density (MRI)	↓ stress, correlated with ↓ right basolateral amygdala grey matter density	MM
House et al. (130)	Mouse cells	In vitro treatment with LSD (100 μm)	Inflammatory markers	↓ proliferation of B-lymphocytes, production of the cytokines IL-2/IL-4/IL-6, induction of cytotoxic T-lymphocytes, NK response, ↑ basal and IL-2-augmented NK cell function	P

(Continued)

TABLE 1 | Continued

Study	Sample (size)	Design/Intervention	Construct (measure)	Findings	MM/P
Huffziger and Kuehner (131)	Depressed patients 3.5 years after discharge from inpatient treatment (N=76)	BS; Negative mood induction + rumination (group 1), distraction (group 2), or mindful self-focus (group 3)	Depression (SCID-I); Coping styles (RSQ); Mindfulness (FMI); Mood (PANAS)	Negative mood group 2-3 < group 1; High mindfulness facilitates negative mood reduction in group 3	MM
Jha et al. (132)	Experimental mindfulness-naive participants (group 1; n=17), experienced meditators (group 2 n=17) and a mindfulness-naive control group (group 3; n=17)	BS; group 1 participated in an 8-week MBSR course, while group 2 participated in a 1-month intensive mindfulness retreat	Alerting/orienting/conflict monitoring (ANT)	Pretraining: group 2 > 1 conflict monitoring; post-training: group 1 ↑ endogenous orienting; group 2 ↑ exogenous alerting	MM
Jimenez et al. (133)	College students (N = 514)	Observational, cross-sectional study; Structural equation modeling to test the relationship between self-rated dispositional mindfulness and depressive symptoms through emotion regulation, mood regulation and self-regulation	Positive emotions (mDES), Perceived mood repair ability (NMR-15); Self-acceptance (PWBS); Mindfulness (FMI); Depressive symptoms (CES-D)	Relationship between mindfulness and depressive symptoms was mediated by emotion regulation, mood regulation and self-regulation. Higher levels of dispositional mindfulness were associated with higher levels of positive emotions, mood regulation expectancies, and self-acceptance; all were inversely related to depressive symptoms. Self-acceptance was the strongest mediator of mindfulness and depressive symptoms.	MM
Kometer et al. (134)	Healthy participants (N=17)	Randomized, double-blind, 4 sessions: Psi (215 g/kg), ketanserin (50 mg), Psi + ketanserin, placebo	Affect (PANAS), Anxiety (STAI-State), Emotion recognition (FERT); Emotional Go/NoGo Task, EEG	Psi: ↑ positive mood, goal-directed behavior (++ > – cues), positive emotion; ↓ recognition of negative facial expression (blocked by ketanserin), negative sequential emotion, P300 component (valence-dependent)	P
Kraehenmann et al. (135)	Healthy participants (N=25)	Double-blind, WS, 2 sessions: Psi (0.16 mg/kg, p.o.) and placebo	Affect (PANAS) Anxiety (STAI); Amygdala reactivity (amygdala reactivity task; BOLD fMRI)	Amygdala reactivity to negative and neutral stimuli Psi < placebo; this response (after Psi) was related to the Psi-induced ↑ positive affect	P
Kubera et al. (136)	Human blood samples from healthy volunteers (N=19) and major depressed patients with treatment resistant depression (n= 7; N=26)	Treatment with 5-HT (150, 1.5 and 15 μg/mL), PCPA (5 μM), flesinoxan (15 and 1.5 μg/mL), mCPP (27 and 2.7 μg/mL), and ritanserin (50 and 5.0 μg/mL)	Cytokine secretion (LPS, PHA); pro- versus anti-inflammatory capacity of cultured whole blood (IFNγ/IL-10 production ratio)	5-HT: ↓ IFNγ/IL-10 ratio; PCPA: ↓ production of IFNγ and IL-10; mCPP and ritanserin: ↓ IFNγ/IL-10 ratio	P
Kuypers et al. (137)	Healthy participants (N=26)	Naturalistic ayahuasca study; Assessment took place at baseline and 2 h after drinking ayahuasca	Divergent thinking ((PLMT), Convergent thinking (PCT)	Convergent thinking ↓, divergent thinking ↑	P
Lazar et al. (138)	Healthy participants with extensive Insight meditation experience (N= 20) and control participants with no meditation or yoga experience (N= 15)	BS Structural MRI; scanning	Cortical thickness (MRI)	Brain regions associated with attention, interoception and sensory processing were thicker in meditation participants than controls, including the PFC and right anterior insula.	MM
Lee et al. (139)	Male Chinese expert meditators N(FAM)= 11; N (LKM)= 11; male Chinese novice meditators N(FAM)= 11; N(LKM)=11	Cognitive tasks during fMRI scanning	Cognitive processing (CPT); Affective processing (EPT); brain activity (BOLD fMRI); affect (CAS)	FAM was associated with expertise-related behavioral improvements and neural activation differences in attention task performance, in contrast to LKM meditation. Both FAM and LKM practice affected the neural responses to affective pictures: For viewing sad faces, the regions activated for	MM

(Continued)

TABLE 1 | Continued

Study	Sample (size)	Design/Intervention	Construct (measure)	Findings	MM/P
				FAM experts were consistent with attention-related processing, whereas responses of LKM experts to sad pictures were more in line with differentiating emotional contagion from compassion/emotional regulation processes.	
Lengacher et al. (140)	Advanced-stage cancer patients (n=26) and caregivers (n=26; N=52)	BS+WS; modified 6-week, self-study MBSR-C	Perceived stress (PSS); Depression (CES-D); Anxiety (STAI); Psychological and physical symptoms (MSAS); QOL (MOS); Stress markers (salivary cortisol and IL-6)	Patients and caregivers: ↓ cortisol at weeks 1 and 3, ↓ IL-6 levels at week 6; patients: ↓ stress, anxiety; caregivers: ↓ psychological symptoms, ↑ QOL (not significant);	MM
Lewis et al. (141)	Healthy participants (N=58)	Double-blind, BS (Psi dose)+WS, 2 sessions: group 1: 0.160 mg/kg Psi p.o.; group 2: 0.215 mg/kg Psi p.o., and placebo	perfusion changes (fMRI); subjective drug effects (5D-ASC)	Group 1 < 2 ↑ subjective drug effects; Psi: ↑ relative perfusion in right hemispheric frontal and temporal regions and bilaterally in the anterior insula, ↓ relative perfusion in left hemispheric parietal and temporal cortices subcortical regions, widespread ↓ in absolute perfusion	P
Lutz et al. (142)	Healthy participants (experimental: n=24; control: n=22)	BS: short mindfulness intervention, followed by emotional expectation paradigm during fMRI scanning	Psychometric measures (SDS; STAI; Eysenck Personality Inventory; EPI; FMI; MAAS) Brain activity (fMRI);	Mindfulness intervention: ↑ activations in prefrontal regions during expectation of (potentially) negative stimuli, ↓ activation in amygdala and parahippocampal gyrus during perception of negative stimuli; prefrontal and right insular activations when expecting negative pictures correlated negatively with trait mindfulness	MM
Ly et al. (143)	In vitro: cultured cortical rat neurons; *in vivo*: Drosophila larvae, zebrafish embryos	In vitro studies: treatment of cultured cortical rat cells with different psychedelic class compounds (amphetamines, ergolines, tryptamines, iboga); *in vivo* studies: administration of DMT or ketamine (10 mg/kg)	Structural change (fluorescence microscopy); Functional change (electrophysiology); Neuroplasticity (BDNF levels)	Serotonergic psychedelics: ↑ neuritogenesis, spinogenesis, synapse number and function; induced structural changes appear to result from stimulation of the TrkB, mTOR, and 5-HT2A signaling pathways.	P
MacLean et al. (144)	Healthy, hallucinogen-naïve participants (N= 52)	Pooled data analysis; Combination of Psi data from Griffiths et al. (102) and Griffiths et al. (82)	Personality (NEO-PI)	Psi: ↑ Openness; In participants who had mystical experiences during their psilocybin session, Openness remained significantly higher than baseline more than 1 year after the session.	P
Malarkey et al. (145)	University faculty and staff (n=186) with elevated CRP level (> 3.0 mg/ml) who had, or were at risk for cardiovascular disease	BS; 2-month MBI-ld (group 1) or lifestyle education programme (group 2)	CRP; IL-6; cortisol; Perceived stress (PSS); Depression (CES-D); Sleep quality (PSQI)	Group 1 > 2: ↑ mindfulness at 2-months and up to a year	MM
Mason et al. (95)	Healthy participants (before ingesting P N=55; the morning after P: N=50); 7 days after P: N=22)	WS; ingestion of truffles (1.9 mg, p.o.) containing Psi in a retreat setting	Creative thinking (PCT), empathy (MET), Satisfaction with life (SWLS)	Psi ↑ divergent thinking & emotional empathy the morning after use; 7 days after Psi: ↑ convergent thinking, valence-specific emotional empathy, and well-being; changes in empathy correlated with changes in wellbeing	P
Matousek et al. (146)	Women with breast cancer and depressive symptoms (N=33)	WS; MBSR programme	Stress (CAR; PSS); Depression (CES-D); medical symptoms (MSCL)	Prolonged ↑ CAR, ↓ self-reported stress levels, depressive symptomatology, medical symptoms	MM
Moore and Malinowksi, (147)	Experienced Buddhist meditators (N= 25) and a	Observational study	Mindfulness (KIMS); degree of automatization/ deautomatization (Stroop task); Attentional	Attentional performance and cognitive flexibility were positively related to meditation practice and levels of mindfulness	MM

(Continued)

TABLE 1 | Continued

Study	Sample (size)	Design/Intervention	Construct (measure)	Findings	MM/P
	meditation-naïve control group (N= 25)		performance and flexibility (d2-concentration and endurance test)		
Mrazek et al. (148)	Healthy undergraduate students (N=48)	WS; 2-week mindfulness-training course	WM capacity (OSPAN); Mind wandering (Thought sampling); Reading comprehension (GRE)	Mindfulness training: ↑ reading comprehension; WM capacity, ↓ mind wandering; improvements in performance were mediated by reduced mind wandering among participants prone to distraction at pretesting	MM
Nau et al. (149)	Young adult male mice	BS; sterile saline or (R)-DOI, followed by TNF-α; pretreatment with a 5-HT2A receptor antagonist. in some mice	Gene expression; protein expression; cytokines	(R)-DOI: ↓ inflammation by blocking the systemic effects of TNF-α (blocked by pre-treatment with a 5-HT2A receptors antagonist)	P
Oken et al. (150)	Community-dwelling caregivers of close relatives with dementia (N=28)	BS, 7 weeks: MBCT-based programme (group 1), education class based on Powerful Tools for Caregivers (group 2) or respite	Stress (RMBPC); mood (CES-D); fatigue (SF-36); self-efficacy (General Perceived Self-Efficacy Scale); mindfulness (MAAS, FFNJ); cortisol; cytokines; cognitive function (10-word list learning task, Stroop task, ANT); expectancy of improvement; credibility of the interventions	Group 1 and 2: ↓ stress, ↑ self-efficacy, cognitive function; significant correlations between mindfulness and self-rated mood and stress scores	MM
Pokorny et al. (151)	Healthy participants (N=32; N(MET)=32; N(MDT)= 24)	Double-blind, WS, 2 sessions: Psi (0.215 mg/kg, p.o), placebo	Empathy (MET, IRI); Moral decision-making (MDT); Affect (PANAS)	Psi > placebo: ↑ emotional empathy	P
Preller et al. (152)	Healthy participants (N=21)	Double-blind, WS, 2 sessions: Psi (0.215 mg/kg, p.o.) and placebo, followed by exposure to social ostracism	Neural activity (fMRI); Empathy (MET)	Psi: ↓ ACC response to social ostracism, ↑ emotional empathy compared to placebo	P
Quednow et al. (153)	Healthy participants (N=16)	Double-blind, randomized, BS: placebo, ketanserin (40 mg, p.o.), Psi (260 mg/kg, p.o.), or Psi + ketanserin	Sensorimotor gating (prepulse inhibition of the acoustic startle response); psychopathological core dimensions (5D-ASC); behavioral inhibition (Stroop task)	Psi: ↓ sensorimotor gating, behavioral inhibition, ↑ all 5D-ASC scores (blocked by ketanserin)	P
Raes et al. (154)	Healthy participants (N(study 1)=164; N(study 2)=39; n(MBCT)=18; n(waiting list)=21)	Study 1: Cross-sectional design to examine the relationship between trait mindfulness and CR; study 2: 8-week MBCT programme or waiting list; BS	Mindfulness (KIMS), CR (LEIDS-R, BDI, MDQ)	Trait mindfulness is negatively correlated with CR; MBCT: ↓ CR (mediated by a positive change in mindfulness skills)	MM
Roseman et al. (155)	Treatment-resistant depression patients (moderate to severe) (N=20)	Open-label, WS, 2 sessions: Psi (10 mg/kg p.o.) and (25 mg/kg p.o.)	Depression (HAM-D, BDI); Amygdala activity to emotional faces (fMRI); Treatment response (in-scanner rating of depressed mood; QIDS)	Psi: ↓ depressive symptoms, ↑ responses to fearful and happy faces in the right amygdala; amygdala(r) increases to fearful versus neutral faces were predictive of clinical improvements at one week	P
Roseman et al. (156)	Healthy participants (N= 40; N(Psi)= 15; N(MDMA)=15)	Pooled data analysis; data from 2 previously published BOLD-weighted fMRI data sets after placebo-controlled administration of Psi (N = 15) and MDMA (N = 25)	Resting-state functional connectivity (RSFC); Subjective effects	Psi> MDMA: changes in consciousness. Psi ↑ between-network RSFC and ↓ RSFC between visual and sensorimotor resting state networks. MDMA had a notably less marked effect on between-network RSFC	P
Ross et al. (97)	Patients with cancer-related anxiety and depression (N=29)	Double-blind, WS, 2 sessions: Psi (0.3 mg/kg, p.o.) and niacin (p.o.), both + psychotherapy	Anxiety and depression (HADS, STAI, BDI)	Psi: anxiolytic and anti-depressant effects which sustained for 6.5 months; effects were mediated by P-induced mystical experience	P
Sampedro et al. (157)	Healthy participants with prior experience with ayahuasca (N=16)	Open-label, uncontrolled, 1 session: ayahuasca (148 mL; 0.3 mg/ml DMT)	Neurometabolic and connectivity modifications (magnetic resonance spectroscopy); mindfulness (FFMQ, EQ, Self-Compassion questionnaire); acute subjective drug effects (HRS)	↓ Neurometabolism in PCC; ↑ PCC-ACC connectivity; ↑ ACC-right MTL connectivity, correlating with ↑ self-compassion; ↓ glutamate + glutamine, correlating with ↑ nonjudging	P

(Continued)

TABLE 1 | Continued

Study	Sample (size)	Design/Intervention	Construct (measure)	Findings	MM/P
Smigielski et al. (158)	Healthy, experienced meditator subjects (N=38; 23 males)	Five-day mindfulness retreat; Single dose of PSI (0.315 mg/kg, p.o.)	Pre- and post PSI brain dynamics during resting state and two meditation forms	Decoupling of mPFC and posterior cingulate cortices: associated with PSI-induced subjective ego dissolution The extent of ego dissolution and brain connectivity predicted positive changes in psycho-social functioning of participants 4 months later PSI + MM facilitated neurodynamic modulations in self-referential networks	P and MM
Stroud et al. (159)	Patients with treatment-resistant depression (n=17) and controls (n=16; N=23)	BS (patient/control)+WS, 2 sessions: Psi 10 mg/kg, p.o. and 25 mg/kg, p.o.	Depression (QIDS); emotional processing (Dynamic Emotional Expression Recognition Task); anhedonia (SHAPS)	Baseline: patients < controls emotion recognition speed; Psi: ↑ emotion recognition speed compared with baseline in patient (correlated with ↓ anhedonia), but not controls	P
Studerus et al. (160)	Healthy participants (N= 110)	Pooled data analysis; Eight double-blind placebo-controlled experimental studies conducted between 1999-2008; 1–4 administrations of Psi (45–315 mg/kg p.o.)	Psychedelic experience (5D-ASC); Mood (AMRS), long-term drug effects (investigator-constructed follow-up questionnaire)	Psi dose-dependently induced changes in mood, perception, thought and self-experience; most participants described the experience as pleasurable, enriching and non-threatening.	P
Surawy et al. (161)	Chronic fatigue syndrome patients waiting to receive cognitive behavior therapy (N=9)	WS; 8-week MM programme	Fatigue (Chalder fatigue scale); Physical functioning (SF-36); Anxiety/Depression (HADS); Effect of fatigue on QOL (FIS)	↓ fatigue, anxiety, depression; ↑ QOL, physical functioning; effects were sustained for 3 months	MM
Soler et al. (162)	Healthy participants with no prior meditation experience (N=20; n(ayahuasca)=10; n (MBSR)=10)	WS+BS(ayahuasca/MBSR); 4 closely spaced consecutive ayahuasca sessions or 8-week MBSR programme	Mindfulness (FFMW, EQ)	MBSR > ayahuasca: ↑ mindfulness; MBSR = ayahuasca: ↑ acceptance	P and MM
Szabo et al. (163)	Human primary moDCs and autologous naïve T cells	In vitro pre-treatment with DMT and a sigmar-1 agonist, followed by inflammatory response induction with LPS (500 ng/mL), polyI:C (20 μg/mL) or pathogen-derived stimuli versus resting state	Cytokines; gene expression; protein expression	DMT: ↓ inflammatory responses, ↑ anti-inflammatory responses in LPS or polyI:C-stimulated moDCs through the sigma-1 receptor	P
Turton et al. (164)	Healthy psychedelic-experienced volunteers (N= 15)	Qualitative study; Psi (2 mg, IV)	Psychedelic experience (Semi-structured interview)	Reports of perceptual changes (visual, auditory and somatosensory distortions), cognitive changes, mood changes, spiritual or mystical type experiences	P
Vollenweider et al. (165)	Healthy participants (N=10)	WS, 3 sessions: Psi (15, 20 mg) and placebo	CMRglu (PET, FDG); ego pathology (EPI); psychopathology (AMDP); subjective drug effects (APZ)	Psi: global ↑ CMRglu, especially in PFC, ACC, and temporomedial cortex and putamen (correlated positively with hallucinatory ego disintegration)	P
Wachs and Cordova (166)	33 married couples (N= 66)	No intervention	Mindfulness (MAAS); Emotional skills and traits (TAS-20, IRI, SECS, ECQ); Marital quality (DAS, Marital Satisfaction Inventory—Revised)	Mindfulness was associated with marital quality and partners' emotion skills. The association between mindfulness and marital quality was mediated by emotion repertoire skill.	MM
Winnebeck et al. (167)	Depressed patients with a chronic/recurrent lifetime history (N=74)	BS; brief MBI or control condition	Depression (SCID, BDI); ruminative tendencies (RSQ); mindfulness (FFMQ); Cognitive reactivity to sad mood (LEIDS-R)	MBI: ↑ mindfulness, ↓ ruminative tendencies, cognitive reactivity; MBI > control ↓ depressive symptoms	MM
Zeidan et al. (74)	Healthy participants, no prior meditation experience (N=63)	BS, 4 sessions: MM training (group 1) or listening to a recorded book (groups 2)	Mood (POMS); Mindfulness (FMI); Depression (CES-D); anxiety (STAI); Verbal fluency (Controlled Oral Word Association Test); Visual coding (DSST); WM (DSST, N-back task); Immediate memory span	Group 1 and 2: ↑ mood; MM training: ↓ fatigue, anxiety, ↑ increased mindfulness, visuo-spatial processing, WM, executive functioning	MM

(Continued)

TABLE 1 | Continued

Study	Sample (size)	Design/Intervention	Construct (measure)	Findings	MM/P
			(forward/backward digit span); Information processing speed and attention (N-back task)		
Zeidan et al. (168)	Healthy undergraduate students with no prior meditation experience (N=82)	BS, 3 sessions: MM training (group 1), sham MM training (group 2), or control condition (group 3)	Mood (POMS); Anxiety (STAI); Heart rate	Group 1 > group 2-3: ↓ negative mood, depression, fatigue, confusion, heart rate	MM

Footnote to clarify the used abbreviations: (R)-DOI, 2,5-Dimethoxy-4-iodamphetamin; 5D-ASC, 5-Dimensional Altered State of Consciousness Rating Scale; 5-HT, Serotonin; ACC, Anterior cingulate cortex; AMDP, Inventory of the Association for Methodology and Documentation in Psychiatry; AMRS, Adjective Mood Rating Scale; ANT, Attention Network Test; APZ, Altered States of Consciousness; ARCI, Addiction Research Center Inventory; ASPIRES, Assessment of Spirituality and Religious Sentiments; BDI, Beck Depression Inventory; BI, Backward inhibition; BPRS, Brief Psychiatric Rating Scale; BSI, Brief Symptoms Inventory; CAR, Cortisol awakening response; CAS, Chinese Affect Scale; CBF, Cerebral blood flow; CEN, Central executive network; CES-D, Center of Epidemiological Studies Depression Scale; CMRglu, Cerebral metabolic rate of glucose; CR, Cognitive reactivity; CPT, continuous performance test; CRP, C-reactive protein; CRS, Competitor Rule Suppression; DAS, Dyadic Adjustment Scale; DASS-21, Depression Anxiety Stress Scale; DERS, Difficulties in Emotion Regulation Scale; DHEAS, Dehydroepiandrosterone-sulfate; DMN, Default-mode network; DMT, N,N-Dimethyltryptamin; DSST, Digit symbol substitution task; DXM, Dextromethorphan; ECQ, Emotional Control Questionnaire; EEG, Electroencephalogram; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EPI, Ego Pathology Inventory; EPT, emotion-processing task; EQ, Experience Questionnaire; ESM, Experience Sampling Method; FACIT, Functional Assessment of Chronic Illness Therapy; FAM, Focused Attention Meditation; FAIR, Frankfurt Attention Inventory; FDG, [F-18]-fluorodeoxyglucose; FERT, Facial Emotional Recognition Task; FFMQ, Five Facet Mindfulness Questionnaire; FFNJ, Measure of being nonjudgmental adapted from factor five; FIS, Fatigue Impact Scale; FMI, Freiburg Mindfulness Inventory; fMRI, Functional Magnetic Resonance Imaging; FNE, Fear of Negative Evaluation Scale, GAF, Global Assessment of Functioning; GRE, Graduate Record Examination; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; HRS, Hallucinogen Rating Scale; IFNγ, Interferon gamma; IL, Interleukin; IMS, Investment Model Scale; IRI, Interpersonal Reactivity Index; KIMS, Kentucky Inventory of Mindfulness Skills; LAP, Life Attitude Profile; LEIDS-R, Leiden Index of Depression Sensitivity; LKM, Loving-kindness meditation; LOT-R, Life-, Orientation Test—Revised; LPS, Lipopolysaccharides; LSD, Lysergic acid diethylamide; MAAS, Mindful Attention Awareness Scale; MACAM, Measure of Awareness and Coping in Autobiographical Memory; MADRS, Montgomery–Åsberg Depression Rating Scale; MBI, Mindfulness-Based Intervention; MBI-ld, low-dose MBI; MBSR-C, MBSR programme for cancer; mCPP, m-chlorophenylpiperazine; mDES, Modified Differential Emotions Scale; MDT, Moral Dilemma Task; MET, Multifaceted Empathy Test; moDCs, Monocyte-derived dendritic cells; MOS, Medical Outcomes Studies Short-Form General Health Survey; mPFC, Medial prefrontal cortex; MSAS, Memorial Symptom Assessment Scale; MSCL, Medical Symptom Checklist; MSI-BPD, McLean Screening Instrument for BPD; MTL, Medial temporal lobe; NEO-PI, Big Five Personality Inventory; NK, Natural killer; NMR-15, Negative Mood Regulation Expectancies scale; OSPAN, Operation Span Task; PANAS, Positive and Negative Affect Schedule; PCC, Posterior cingulate cortex; PCPA, P-chlorophenylalanine; PCT, Picture Concept Test; PEQ, Persisting effects questionnaire; PFC, Prefrontal cortex; PHA, Polyhydroxyalkanoate; PILT, Purpose in Life Test; PLMT, pattern/line meanings test; PLOT, Penn Line Orientation Test; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; PWBS, Psychological Well-Being Scale; QIDS, Quick Inventory of Depressive Symptoms; QOL, Quality of Life; RCOPE, Religious Coping Activity Scales; ReSSI, Relapse Signature of Suicidality Interview; RMBPC, Revised Memory and Behavior Problems Checklist; RRQ, Rumination–Reflection Questionnaire; RSQ, Response Styles Questionnaire; SCID, Structured Clinical Interview for DSM-5; SCL-90, Symptom Check List-90; SCS, Self-Control Scale; SDS, Self-Rating Depression Scale; SECS, Self-Expression and Control Scale; SF-36, Short Form 36; SHAPS, Snaith-Hamilton Pleasure Scale; SOCQ, Selection-Optimization-Compensation Questionnaire; SOSI, Symptoms of Stress Inventory; STAI, State-Trait Anxiety Inventory; SWLS, Satisfaction with Life Scale; TAU, Treatment as usual; TAS-20, Toronto Alexithymia Scale; TMMS, Trait Meta-Mood Scale; TNF-α, Tumour necrosis factor alpha; WM, Working memory.

personal insights and enduring positive mood effects. Likewise, positive mood state following personal insights during a psychedelic experience might, facilitate the non-judgmental observation of negative thoughts, since previous research suggests a bidirectional positive relationship between positive mood and mindfulness (121).

Whether the single or combined practice in psychiatric patients would be beneficial is another question. Two recent studies investigating the effects of ayahuasca, another psychedelic substance with similar 5-HT2A agonistic action as psilocybin was shown to increase emotion regulation and some aspects of mindfulness in healthy volunteers (162, 118). Of note, mindfulness was not increased in participants with borderline personality disorder traits (118). This may bear meaningful clinical implications, as people with certain psychopathologies, including depression, might be less receptive to a psychedelic-induced enhancement of mindfulness.

Executive Functioning

Studies have demonstrated positive effects of MM on executive functioning, including improvements in cognitive flexibility (122). Repeated training of mindfulness has been shown to improve WM as well as attentional and inhibitory capacities (74, 123, 132, 147, 148).

A possible explanation for MM-induced executive function enhancement builds on an incremental reduction of mind-wandering together with an enhancement of meta-awareness. The former describing the tendency to drift off with one's thoughts, while the latter can be conceptualized as the acknowledgement of ongoing mental processes, which shares a neural signature with that of executive functions. Accordingly, this hypothesis was supported empirically (74, 126, 149). A positive "side" effect of MM's cognition-enhancing effects is a more pronounced subjective sense of control, as shown in a study investigating the effects of MBSR (105).

In contrast to MM's homogenously positive effects across cognitive domains, psilocybin tends to acutely impair some aspects of executive functioning like inhibition, attention, and WM (93, 115, 116, 153), while improving others by, for example, inducing a greater bias towards positive stimuli (134), or leaving some processes unaffected, like spatial WM (107, 115, 116, 153).

The feeling of loss of control over thoughts or perceptions is frequently reported in psilocybin trials, which is linked to adverse reactions, and may reflect the induced decreases in executive control (128, 160, 164). On the other hand, psilocybin's dys-executive effects have also been proposed to offer therapeutic implications as to surface suppressed emotions and thoughts in order to confront them and, hence, restore emotional responsiveness in MDD (155).

Further, consistent with the notion that psilocybin impairs cognitive focus and control, 5-HT2A agonism has been implicated in an acute decline in convergent thinking, which critically relies on adequate executive functioning (137). In line with this, it was shown that LSD-induced impairment of working memory, executive functions, and cognitive flexibility was mediated by the 5-HT2A receptor (174). Conversely, 5-HT2A agonism is also associated with increased cognitive flexibility and divergent thinking (106, 119, 127, 137, 144, 175). The latter findings might be suggested to underlie decreased executive control and a loosening of associations *via* neuroplastic changes in core neural networks, although this hypothesis has to be tested. Additionally, it is suggested that these psychedelic-induced increases in cognitive flexibility are potentially long-lasting (119, 127, 144).

Taken together, MM demonstrates relatively global cognition-enhancing effects upon repeated training, whereas psilocybin's effects on executive functioning build on increased acute disinhibition and enduring cognitive flexibility (**Figure 2**). Supporting psilocybin-assisted therapy with MM practice may have the potential to buffer feelings of loss of control associated with the acute psychedelic effects by boosting both subjective and objective executive functioning and, consequently, reducing the risk of adverse reactions. Alternatively, an interference with the individual effects of either treatment is also possible. For instance, by improving cognitive control, MM may reduce psilocybin's cathartic effects or, conversely, psilocybin might exacerbate the practice of MM during acute effects, as certain aspects of mindfulness, especially in FAM, build on attentional capacities (139).

Social Skills

With regard to social skills, MM has been linked to greater relationship satisfaction, as it supposedly fosters a more adequate expression and recognition of feelings and reduces the degree to which an individual is emotionally affected by distressing social events (107, 166, 169). This led to the emergence of variants of MBIs that specifically focus on the interpersonal aspects of MM, such as mindful relating (166) or mindfulness-based relationship enhancement (MBRE) (176). These trainings are encompassed by the frame term "relational mindfulness" and lay emphasis on fostering compassion and attentive communication to others.

Psilocybin has positive acute and subacute effects on some aspects of empathy (95, 151, 177). A recent study (159) further showed that psilocybin improved emotional face recognition (cognitive empathy) in TRD patients, while another study demonstrated reduced feelings of social exclusion and in healthy volunteers following psilocybin administration compared to placebo (153).

Pahnke (171) suggested that, in the afterglow, the willingness "to enter into close interpersonal relationships" may be heightened, which is in agreement with self- and other reports of positive changes in social attitudes and behavior following psychedelic peak experiences (69, 88, 96, 102). One aspect of peak experiences in particular, namely the phenomenon of ego dissolution, could be meaningful in this context. Ego dissolution can be described as the loss of sense of identity that is separate from its surroundings and is, therefore, accompanied by an intense feeling of connectedness with the environment. Such an experience may contribute to the destabilization of self-centered belief systems and open the individual up to his or her social surroundings (172). This theoretical implication is supported by the finding of enduring increases in the personality trait "openness" following a psilocybin session (69, 144).

Both MM and psilocybin appear to induce long-term enhancements of social skills. Based on studies conducted up

until now it is suggested that MM does so by influencing the way an individual deals emotionally with social encounters, which, as a result, promotes adequate social behavior, or interpersonal social skills. Psilocybin seems to predominantly act on an intrapersonal level of social skills by means of enhanced empathic abilities and a changed personality (**Figure 2**). Combining MM and psilocybin could potentially enhance social relationships more efficiently, as changes in social cognition effectuated by psilocybin would be expected to complement changes in social behavior induced by MM.

BIOLOGICAL FACTORS

Studies have shown a range of biological deficiencies to be implicated in MDD among which impaired neuroplasticity, an imbalance in core neural networks, and disturbances in stress responses which are visible as disruptions in neuroendocrine and neuroimmune parameters (21, 22, 29). In the next section MM and psilocybin effects on these processes are summarized.

Neuroplasticity

For MM, BDNF-promoting effects appear to be linked to prolonged, repeated practice (110) rather than a single, brief training session (125). The exact mechanisms underlying these effects are unclear, though. While MM's relation to serotonin signaling has not been investigated yet (101), the expression of BDNF may be enhanced by either frontal activation following active engagement of attention, vagal stimulation or a reduction in stress response (110).

Psilocybin and related classical psychedelics, such as lysergic acid diethylamide (LSD) or N,N-dimethyltryptamine (DMT), are hypothesized to promote neuroplasticity through mechanisms involving 5-HT2A agonism (67). Serotonin 2A receptors, to which psilocin binds, are especially prominent on large glutamatergic pyramidal neurons in deep cortical layers projecting to layer V pyramidal neurons of the PFC, and on layer V itself. These receptors are suggested to rapidly increase in activity as psilocybin is ingested, hypothetically resulting in an elevated expression of BDNF (67, 143). The resulting temporarily state of heightened neuroplasticity may already occur after a single, psychotropic dose and could allow for major synaptic changes, which was suggested to offer an important opportunity for psychotherapeutic interventions (67).

This indicates that the effects of psilocybin and MM on neuroplasticity differ in aetiology and magnitude. Psilocybin could induce a transient, but powerful neuroplastic boost, which is driven by bottom-up glutaminergic processes. In contrast, MM supposedly relies on top-down regulatory efforts and encourages plasticity incrementally throughout the progress of training (**Figure 2**). These approaches may support one another, as MM could possibly serve to prolong the potential neuroplastic state induced by psilocybin and psilocybin might boost the rate at which BDNF rises throughout MM training.

Neural Core Networks

MM has differential effects on the SN and CEN with SN regions, the insula and anterior cingulate cortex (ACC), being engaged during mediation, whereas the activity of CEN regions, the lateral PFC and parietal cortex, decreases (75). As the insula and ACC are involved in interoceptive processes (178) and the lateral PFC and parietal cortex in external awareness (179), this is thought to reflect inward-focused attention during the practice of mindfulness (75, 77). Moreover, MM promotes the activation of the dorsolateral PFC, a key region of the CEN, which is important for cognitive control (142, 180). Long-term meditators show increased cortical thickness in the insula, sensory cortices, and PFC as well as reduced volume of the amygdala, a region involved in fear responses (129, 138). This supposedly represents decreased emotional over-reactivity and increased regulatory control that has been manifested through repeated practice, which is in line with the effects on mood and executive functioning, as discussed above.

Psilocybin was proposed to globally decrease functional neural integrity within, while increasing connectivity between networks, which may be responsible for the experience of hallucinations, loosening of strong associations, and increases in cognitive flexibility following its administration (112, 156, 175). Most notably, the cortical disintegration of the DMN has been implicated in the occurrence of social skill-related ego dissolution and increases in some aspects of mindfulness (77, 157, 181). In addition, an increased functional connectivity between SN and CEN contrasts the aforementioned effects of MM on these networks (156), which might relate to the treatments' opposing cognitive effects. The glutaminergic action of 5-HT2A receptors discussed in the previous section would suggest that psilocybin induces widespread cortical activations, particularly in association cortices, where 5-HT2A receptors are most abundant (182). Consistent with this expectation, some studies appear to endorse acute psilocybin-induced hyper-activation in frontal regions, as opposed to more posterior regions, and this pattern of activity correlated positively with the measures of psychotic symptoms, especially ego dissolution (106, 141, 165). An fMRI study of psilocybin's acute effects showed deactivations in cortical hub regions, such as the posterior cingulate cortex and thalamus. This could be explained by an involvement of GABAergic interneurons within psilocybin's pathway of action, which, when excited, inhibits subsequent neurons (111). The apparent paradox between the frontal hyper-frontality shown in one study (165) and the decreased perfusion in frontal regions by another study (111) was suggested not to be in contrast, but rather dependent on the method of analysis (141). It was suggested to interpret the relative changes in perfusion in relation to absolute signal variations, and to report two analyses, with and without this "correction" for global activity as a solution to enhance transparency, reduce inconsistencies, and help in the interpretation of findings (141). Nonetheless, as cortical hubs play a crucial role in coordinating the flow of information across functionally discerned brain areas, their inhibition might result in sub-optimal communication between brain areas involved in

executive control, reflecting the disinhibition effects of psilocybin (183).

While jointly working to resolve DMN dominance associated with excessive rumination (22, 23, 77), MM and psilocybin seem to alter circuits differentially. MM additionally targets areas related to interoception and executive control, while psilocybin has a more wide-spread effect on functional integrity, potentially promoting flexible cognition (**Figure 2**). This appears to reflect the MM- and psilocybin-induced psychological changes described earlier. By reorganizing the connectivity between the DMN, CEN and SN, MM, and psilocybin may restore normal functional integration in patients, which could contribute to a reduction of negative and rigid thinking patterns. Relevant in this light is the recent study by Smigielski et al. (158) who administered a single dose of psilocybin (0.315 mg/kg, p.o.) to healthy, experienced meditators, during a five-day mindfulness retreat. The pre-post brain resting state analysis revealed a decoupling of medial prefrontal and posterior cingulate cortices, which was associated with the psilocybin-induced subjective ego dissolution. Of note, the extent of ego dissolution and brain connectivity predicted positive changes in psycho-social functioning of participants 4 months later.

Neuroendocrine and Neuroimmunological Factors

The attenuation of stress responses has been suggested to be a central mechanism through which MM exerts its beneficial effects on mental and physical health. MM may do so by, reducing stress-reactivity, in addition to promoting regulatory prefrontal pathways, involving a reduction in amygdalar projections and HPA axis activity (68). However, although MM training generally reduces subjective psychological stress (140, 150), its effect on cortisol secretion varies across populations. In healthy volunteers, eight weeks of MBSR training had no effect on cortisol levels (145, 150), whereas, in cancer patients, cortisol levels decreased significantly under comparable intervention settings (113, 140).

As diseases represent sources of profound stress, this may imply that the association between MM and cortisol only holds for highly stressful situations, which was supported empirically by Brown et al. (109). Accordingly, it is conceivable that MM also reduces cortisol levels in depressed patients. Instead, what has been observed by Matousek et al. (146) was that MBSR increased the CAR in cancer patients who demonstrated depressive symptoms. This conforms an alternative hypothesis, namely that MM not merely reduces cortisol, but rather optimizes HPA responsivity (78, 184). However, another study investigating the effect of MBCT on the CAR in patients remitted from recurrent depression did not support the findings by Matousek et al. (146) (120), which may be due to the use of MBCT rather than MBSR (78). MBSR, as opposed to MBCT, is implicated in being a particularly suitable means for diminishing overall stress symptomatology, as it promotes specific stress coping strategies (79, 113). Although MM might additionally reduce pro-inflammatory cytokines, including IL-6, these findings are inconsistent (140, 145), but may originate from vagal stimulation, which is thought to induce a cholinergic anti-inflammatory reflex (185).

Psilocybin, on the other hand, is associated with an acute increase in cortisol levels (128). In accordance with the involvement of cortisol in attention and memory, this transient elevation could possibly facilitate extinction learning of negative associations by prioritizing the formation of new memories over the retrieval of older memories (186, 187).

Moreover, psilocybin reduced subjective stress in terminally ill cancer patients during the first three months following administration (99). An incremental down-regulation of 5-HT2A receptors is suggested to play a role in this as prefrontal 5-HT2A receptors were found to be involved in stress response pathways (188). Furthermore, by activating prefrontal areas, psilocybin might encourage top-down control of stress responses in limbic structures, such as the amygdala (67).

5-HT2A agonism has also been linked to major anti-inflammatory action, as 5-HT2A receptors are integrated in an abundance of cells throughout the immune system (149, 189, 190). Psilocybin and related psychedelics are hypothesized to distort cell signaling within the immune system by selectively stimulating anti-inflammatory pathways (191, 192). Although this is yet to be tested with psilocybin, LSD, DMT, and 2,5-Dimethoxy-4-iodoamphetamine (DOI) were found to have anti-inflammatory action, inhibiting the production of IL-6 (130, 149, 163) which might account for enduring antidepressant psychedelics effects (193). Nonetheless, there is evidence that 5-HT2A receptors are also involved in pro-inflammatory responses. The extent to which 5-HT is immunosuppressive or immune-activating may depend on its blood concentration (136).

The neuroendocrine and neuroimmune system are interdependent networks that communicate by means of hormone and cytokine signaling (194). MM and psilocybin act differentially and possibly complementarily on these systems. Through the progressive strengthening of regulatory control and reduction of stress-responsiveness, MM optimizes HPA axis functioning and may, eliminate immune system disruptions. Psilocybin, one the other hand, could transiently reduce inflammatory responses by means of 5-HT2A agonism and consequently reduce the stimulation of the HPA axis through anti-inflammatory cytokines (**Figure 2**).

DISCUSSION

Depression is a major public health problem, to which conventional treatments represent an insufficient solution (1, 45, 51). MM and psilocybin appear to be promising novel treatments, and combined their resulting therapeutic effect might even be greater. However, the current literature is limited to theoretical and empirical underpinnings of their singular use in treatment (e.g., 61, 63). The present review therefore aimed to identify possible additive or complementary effects of MM and psilocybin on six factors (mood, executive functioning, social skills, neuroplasticity, neural core networks, neuroendocrine, and neuroimmunological factors) associated

with MDD in order to offer theoretical implications for future clinical research of depression. Findings showed that MM and psilocybin exerted similar effects on mood, social skills, and neuroplasticity; different effects were found on executive functioning, neural core networks, and neuroendocrine and neuroimmune system markers. The effects on mood were "dose"-dependent, with more MM practice or higher psilocybin doses leading to more pronounced mood effects; effects on neuroplasticity were already visible after a single dose of psilocybin, while more MM practice sessions were needed before effects were visible. While for most factors the combination of MM and psilocybin is potentially beneficial, this was not clear for executive functions.

From a psychological perspective, MM employs mental strategies that augment emotional and cognitive self-regulation in the long term (73, 133, 154), whereas psilocybin has neuromodulatory effects that induce a state of apparent "flexible" cognition, and may lead to personal insights that diminish negative biases (102, 111). A combination of MM and psilocybin could possibly shift both the cognitive frame and content of thoughts towards a more positive, open-minded outlook, promote the feeling of control over strong emotions that might occur under the acute effects of psilocybin, or improve communication skills. This may ultimately enhance psychological factors, such as mood, cognitive control, and relationship satisfaction. Recent research suggests that the extent of psilocybin-induced ego dissolution during a mindfulness session might play a very important role in the endurance of positive changes in psycho-social functioning (158).

From a biological perspective, MM serves to adjust prefrontal and limbic activity and HPA reactivity through repeated top-down control (129, 138, 184). Psilocybin, on the other hand, promotes global network disintegration and anti-inflammatory effects involving transient bottom-up processes (175, 191). Pairing these effects may result in a two-way reorganization of neural networks, especially those involved in rumination, and downregulation of neuroendocrine and neuroinflammatory responses. Part of this suggestion was investigated and supported by a recent study that showed decoupling in self-referential networks and the psilocybin-induced change in self-experience, during a mediation retreat, to be predictive of enduring positive changes in psycho-social functioning (158). Together these findings offer several implications for future clinical research into MDD.

Implications for Future Research

The present findings suggest that the combination of MM and psilocybin could possibly exert larger or longer-lasting effects in the treatment of MDD than either treatment alone. These effects may particularly relate to enhancements in mood, social skills, neuroplasticity, and a reduction of stress-related neuroendocrine and neuroinflammatory markers. Testing this hypothesis requires comparisons of changes in these variables in depressed patient groups in a—preferably—randomized, double-blind, placebo-controlled trial with repeated measurements to test acute and persistent effects, weeks to months after treatment.

Ideally, psilocybin-assisted MBI is compared to psilocybin and MM alone, and to a conventional antidepressant (SSRI). To test the effects of MBI on the variables of interest a "psychological" placebo, e.g., minimal psychological support based on CBT principles, complementing the pharmacological manipulation, is needed. This is also warranted since the administration of psilocybin without psychological support is not recommended (94). Primary endpoints would focus on depressive symptomatology assessed with daily diaries and weekly assessments with the Hamilton Depression Inventory or the Beck Depression Inventory (BDI) (195–197). Secondary endpoints would be social skills and executive functioning, assessed with cognitive tests, self-reports, and structural and functional brain imaging; neuroplasticity (BDNF), neuroendocrine (cortisol, oxytocin) and neuroinflammatory (cytokines) factors assessed in blood samples. To add, self-reports from patients and observational reports from significant others could be used to test whether depressed patients indicate less conflict and higher relationship satisfaction following a psilocybin-assisted MBI than their respective control groups as both treatments are known to alter the perception of social relations (107, 172). Cognitive tests at different time points in the treatment will be useful to dissociate short- and long-term effects of the combination of MM and psilocybin on executive functioning and clarify potential opposing effects on such processes as suggested by the inconclusive findings in the present review.

To date, no norms regarding the exact procedure, type of psychological support, dose(s) of the psychedelic, or duration of the psychedelic therapy have been agreed upon (198). With regard to the psychological component of psilocybin-assisted MBI therapy, the typical treatment duration of eight weeks MBI may be appropriate (78). To add, it has not yet been determined whether MM should precede or follow the administration of psilocybin. The present findings would endorse MM practice prior to a psilocybin session, as it may have the potential to reduce the risk of adverse effects in depressed patients due to its positive effects on mood and cognition (e.g., 74). Moreover, the findings imply that MM could facilitate the occurrence of peak experiences upon psilocybin administration (69), something that has been shown to be important in the treatment response (97, 155).

Considering the potential benefits of these implications, future studies could test if (eight weeks of) MM practice prior to a psilocybin session can decrease potential adverse reactions such as anxiety, and increase the chance of having a peak experience, or increase the intensity of the experience during a psilocybin session, compared to appropriate control conditions (69, 102, 124, 144).

Lastly, a combination of MM and psilocybin may also bear benefits for MDD patients in a more indirect way, as findings indicate. Mindfulness could represent a useful asset to the training of psychedelic therapists (199, 200). Future studies may test if patients of psychedelic therapists trained in mindfulness demonstrate better outcomes on psychological measures of depression in comparison to patients of therapists that were not trained in mindfulness.

Limitations

Upon discussing scientific implications that the findings offer, it is important to mention that the present review features a

number of limitations. First, due to different methodologies, findings of the included studies are difficult to compare. For example, studies examining the effects of MM have used diverse assessment methods to measure similar variables in different populations, which could explain the inconsistent findings across studies. For instance, while Carlson et al. (114) demonstrated positive effects of MBSR on mood states (Profile of Mood States) of cancer patients compared to pre-MM scores, Astin (105) did not demonstrate significant effects of MBSR on mood (Symptom Check List-90-R (SCL-90-R)) in undergraduate students. While the (physical and mental) difference in groups are apparent, the construct differences between questionnaires might not be that obvious. Whereas the POMS is specifically designed to assess mood states, the SCL-90-R screens for a broad range of clinical symptoms (201–203).

Another example is the significant decrease shown in immune markers (salivary IL-6 level) in healthy participants (cancer patient caregivers) after six weeks of MBSR, and the absence of this finding in university staff and students following an 8-week-long low-dose MBI (145). Despite both groups being regarded as healthy, it is apparent that they were exposed to dissimilar kinds of stressors, which precludes inferences about general effects of MM on immune system markers.

Another methodological issue noted in the reviewed MM studies is the general lack of active control groups, which impedes the differentiation of effects that are specific to MM from those that apply to any other psychological treatment. Hence, points of attention when conducting a study investigating the effects of MM are to use gold standard tests to assess certain constructs and the inclusion of active control groups (203).

As for studies investigating the effects of psilocybin there are a number of methodological issues that at this moment withhold from making firm statements about potential implications. Examples are the small number of patients samples (96, 99, 103, 159), the use of an open-label design, and no control group (103). These methodological choices make the generalization of findings to larger populations not possible at this stage, and due to the use of open-label or uncontrolled designs, pharmacological effects cannot be separated from expectancy or placebo effects. Additionally, psilocybin is routinely combined with psychological support, making it difficult to dissociate the psychotropic from general care effects (62, 63, 69).

Moreover there are conceptual issues regarding the definition of MM, as it comprises various forms, such as FAM, MBCT or MBRE. These techniques emphasize different aspects of mindfulness and consequently yield diverse psychological and biological effects (60, 75, 176). For example, the effect of MM on cortisol (CAR) differs between MBCT and MBSR (78, 120). Hence, findings in one study may not necessarily apply to all forms of MM and introduce methodological noise.

With regard to psilocybin, and its mechanism of action, the discussion largely pertained to 5-HT2A agonism (67, 136, 143, 149, 175, 188–191, 204) while psilocybin is also known to act on other neurotransmitter systems (87) which might be relevant for the comparison with MM.

Further, in some of the included papers, hypotheses were proposed that have not been subjected to sufficient empirical testing, such as proposed mechanisms regarding the immunosuppressive action of psilocybin and BDNF-promoting effects of MM (67, 68, 110, 191). To draw definite conclusions, premises based on concrete empirical evidence are needed, and therefore, the inferential power of the present review with regard to the aforementioned is limited. These hypotheses were nevertheless incorporated with other reviewed literature in order to speculate on potential interaction points between psilocybin and MM that may be of value in the treatment of depression upon investigation.

CONCLUSION

The present review provides an extensive overview of the current scientific knowledge on the effects of MM and psilocybin on specific pathological depressive features, and on how both interventions might be complementary or even synergistic when combined, in the treatment of depression. With this a valuable theoretical ground for future research is presented. Future studies investigating these effects in both healthy and depressed populations, using rigorous control conditions and representative samples, will provide more knowledge on possible implementation of psilocybin-assisted MBI in clinical practice.

AUTHOR CONTRIBUTIONS

KH and KK conceptualized the review question. KH conducted the literature search. KH conceptualized the first version and figures. KH and KK wrote the paper.

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