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Psychedelics and the treatment of eating disorders: considerations for future research and practice

Emilie Lacroix[1*], Karsten Fatur[1], Phillipa Hay[2], Stephen Touyz[3] and Aaron Keshen[4]

Abstract

Recent trials have shown promising results for the use of psychedelic-assisted therapies in treating severe refractory psychiatric illnesses, and there has been growing interest in examining the effectiveness of these therapies in treating eating disorders. To move forward in a safe, ethically sound, and scientifically rigorous manner, the field must address critical considerations. In this Comment article, we outline important risks and ethical considerations, along with methodological aspects that require careful consideration in the design of psychedelic-assisted therapy trials. We conclude by providing provisional guidelines for clinical research trials to help shape the future of this work, with the aim of investigating and employing the use of psychedelics for treating eating disorders in a manner that protects clients and research participants while maximizing methodological rigour.

Keywords Eating disorders, Psychedelics, Treatment, Methodology, Ethics

Introduction

After years of stagnation, interest and research in the use of psychedelics and other mind-altering substances for the treatment of mental health conditions have taken off, moving us into what many have called a psychedelic "renaissance" [1]. Though some Indigenous groups have been using psychedelics as part of healing and divinatory rituals since time immemorial, modern scientific investigation and interest from Western medicine in such substances began with the isolation of mescaline from the peyote cactus in 1897 [2], followed by the serendipitous discovery of lysergic acid diethylamide (LSD) in the 1940s [3]. Research increased over the following decades until widespread restrictions were put into place around the globe in the 1970s, due in part to the associations between psychedelic substances and counter-cultural movements of the 1960s [4, 5], as well as concerns about the risks of psychosis [6] and dependency [7]. Research before this time was marred by severe methodological and ethical issues including flawed study designs that lacked proper controls, blinding, and informed consent procedures, making it nearly impossible to draw conclusions from the data. Research began again in the 1990s, and has bourgeoned in more recent years [8]. The contemporary return to the topic, however, seeks to correct the errors that plagued previous work, and has led to promising findings in the treatment of mental health conditions such as depressive disorders, substance use disorders, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder [9].

*Correspondence:
Emilie Lacroix
elacroix@unb.ca
[1]Department of Psychology, University of New Brunswick, 38 Dineen Drive, Fredericton, NB, Canada
[2]Translational Health Research Institute, School of Medicine, Western Sydney University, Campbelltown, Australia
[3]Inside Out Institute, University of Sydney, and Sydney Local Health District, Sydney, NSW, Australia
[4]Department of Psychiatry, Dalhousie University, 5909 Veterans Memorial Lane, Halifax, NS, Canada

Classical psychedelics are substances such as psilocybin, LSD, mescaline, and *N*, *N*-dimethyltryptamine (DMT) that have agonist activity on 5-HT_{2A} serotonin receptors, which can lead to neural impulses accessing new areas of the brain [10, 11]. Such substances may profoundly affect perception, cognition, and emotion, and the effects often lead to spiritual and/or perceived psychologically insightful experiences [12–14]. Psychedelics may also promote neuroplasticity, the functional and structural changing of the brain; indeed, this is thought to be part of their therapeutic benefit [15, 16].

Other substances—despite not technically being psychedelics—are often referred to under this label, especially those that have been classified under the broader umbrella category of "hallucinogens" in which classical psychedelics are also located; for example, 3,4-methylenedioxy-methamphetamine (MDMA)—an empathogen with multiple mechanisms of action—and ketamine—a dissociative anesthetic that functions as a glutamate antagonist at N-methyl-D-asparate (NMDA) receptors—are often referred to as psychedelics [17, 18]. Though these substances have different mechanisms of action and effects, we will refer to them under the broader umbrella of *psychedelics* throughout this paper in line with current trends and to match the bulk of current literature we will be drawing on; we use the term *classical* psychedelics to refer to serotonergic psychedelics.

Contemporary psychedelic practice does not merely involve the administration of mind-altering substances as with traditional psychiatric medications. Psychedelic medicines are administered in large doses, leading to more noticeable effects while they are active, and are combined with psychotherapy from a trained practitioner within the context of a brief intervention [19]. This means that the profound psychedelic experiences are intended to be embedded within a safe clinical setting where their benefits may be most optimally reaped and focused on underlying psychopathology, thus potentially leading to improvements in wellbeing and reductions in psychiatric symptoms [9, 20]. Such treatments are often referred to as psychedelic-assisted therapies (PAT), and their effectiveness is thought to hinge on a range of variables, especially client preparation and the therapeutic setting [21].

Promising results from clinical trials have led to a great deal of public and commercial interest. To hasten the drug development and review process, the United States Food and Drug Administration has granted "breakthrough therapy" status for psilocybin in the treatment of depression, as well as for MDMA in the treatment of PTSD [19, 22]. Similarly, in Australia psilocybin and MDMA have been approved by the Therapeutic Goods Administration for use in the treatment of depression and PTSD [23]. Though findings are varied, the literature contains many studies with encouraging results for the treatment of depression, PTSD, and substance use disorders, among others [24–26].

Research into psychedelic treatment of eating disorders, which has been thoroughly reviewed elsewhere [19, 27, 28], has lagged behind developments in the treatment of other mental health concerns. As the pathophysiology of eating disorders is lesser known [29], it is difficult to determine what mechanism of action may be responsible for benefits that may arise with PAT [19]. As such, there are multiple potential mechanisms that may be especially important for clients struggling with eating disorders, including biochemical effects directly related to 5-HT_{2a} agonism, changes at the brain network level (including changes in functional connectivity and neuroplasticity), improved cognitive flexibility, and improvements in symptoms of comorbid conditions and in quality of life [19]. Furthermore, PAT may serve to break down maladaptive beliefs or thought patterns related to one's body and shape, to normalize reward processing, reduce behavioural and cognitive rigidity, and aid in trauma processing [19, 20, 27, 30–32]. As with other mental health conditions, another potential benefit is the way that psychedelics may induce mental states conducive to engaging in the therapeutic process [28].

At the time of writing, there are at least six registered clinical PAT trials underway for the treatment of eating disorders across North America, Australia, and Europe. All of these trials are examining the potential use of psilocybin; four of these are focused on anorexia nervosa, one on binge eating disorder, and one on body dysmorphic disorder [28].

Though PAT presents exciting potential in the future of eating disorder research and treatment, some critical considerations must be meaningfully addressed for the field to move forward in a manner that is both ethically sound and scientifically rigorous. In this article, we share our hope and excitement for the future of this field, and lay out risks and ethical considerations tied to this form of treatment. We conclude by offering provisional guidelines for clinical research that may help in shaping the future of this work, in the hopes that the use of PAT for eating disorders is investigated and employed in an appropriate and rigorous manner.

Potential risks

Risks associated with psychedelic medicines

Classical psychedelics (LSD, psilocybin, DMT, mescaline) are thought to be largely quite safe, with low risks of adverse events, especially in clients who have been appropriately screened and psychologically prepared; even in uncontrolled settings, toxicity is rare [33–35], and these substances are thought to have a low abuse potential [34]. When they do arise, adverse events tend

to be tolerable and resolve once the effects of the substance have worn off [36]. Downey et al. [37] reviewed safety considerations for psilocybin therapy and anorexia nervosa, as well as risk mitigation strategies. Adverse effects still occur with serotonergic psychedelics; commonly, these may include nausea, dizziness, and headaches, as well as tachycardia and hypertension [11, 33]. The most common adverse effects, however, are transient psychologically challenging experiences ("bad trips"), occurring in 26–63% of administrations in modern trials; such experiences may include periods of intense anxiety or paranoia and can be unpleasant for the client [38, 39]. Some have reported these experiences to have putative benefits when the individual is prepared and able to work through them and make meaning from their occurrence [40]; cultivating an appropriate mental set and physical setting to reduce this risk is important in PAT treatments with any psychoactive medicine.

Unlike these medicines previously discussed, MDMA is not a classical psychedelic, but rather has been deemed an "enactogen" or "empathogen," thus named because of its tendency to heighten empathy and feelings of social connection in those under its influence [41–44]. MDMA affects a range of neural pathways, including those related to serotonin, dopamine, and noradrenaline [45]. Its use in PAT is thought to be safe in healthy subjects within a controlled clinical setting, though it is important to note that it carries abuse potential and is thought by some to have habit-forming potential [46, 47]. The use of MDMA carries with it many potential unwanted side effects, including hypertension, tachycardia, and hyperthermia, which can be severe and life-threatening in some rare circumstances [48, 49]. Dizziness, headache, nausea, anxiety, heart palpitations, and other effects may also occur [47]. In addition to these effects that occur during the MDMA experience, this substance often leaves individuals with a short-term and transitory period of depression, anxiety, and insomnia once the effects have worn off; though these lingering effects are generally mild, they may present a problem for those with existing low mood, and can lead to suicidal ideation and attempts [42, 50].

Representing yet another class of compound, ketamine is technically classified as a dissociative anaesthetic and is a non-competitive antagonist of the NMDA receptor; it also interacts with a range of other systems, including opioid, monoamine, and cholinergic receptors [51, 52]. This substance was traditionally used in animal and emergency anaesthesia, a use that remains popular to this day [53]. Unlike the other psychedelic medicines, ketamine is also used as a regularly administered medicine in sub-psychedelic doses [54]. As with the other psychedelic medicines, ketamine also has the potential to cause adverse side effects; these may include transitory stimulatory hemodynamic effects [55]. Long-term risks of cognitive harm and damage to the bladder are also possible with ketamine, though these have been reported by recreational users rather than clients receiving ketamine for medical purposes [56, 57], suggesting these symptoms may be linked to contaminated supply, rather than to ketamine itself. Ketamine is also a widely used recreational substance that carries potential for abuse and habit-forming potential effects [58]. As with the classical psychedelics, the risk of a "bad trip" is present with both MDMA and ketamine, in addition to their physiological risks [47, 59].

One area of concern is the potential for long-term perceptual distortions due to psychedelic use, such as episodes of visual distortions or flashbacks occurring beyond the psychedelic experience itself. Such symptoms were frequently reported in early research with psychedelics [60–63]. In severe cases, a diagnosis of hallucinogen persisting perception disorder may be warranted. In addition to the serotonergic psychedelics, MDMA is also known to potentially trigger hallucinogen persisting perception disorder [64, 65]. Cases of hallucinogen persisting perception disorder have been only rarely reported, and none, to our knowledge, have been reported in modern clinical trials. Thus, it is thus thought to be uncommon [47, 66]. As previously mentioned, early psychedelic research was neither methodologically nor ethically sound. Modern practices with better screening and exclusion criteria as well as more rigorous study designs have yielded far fewer occurences of long-term perceptual distortions. For example, no contemporary trials have reported the development of lasting flashbacks in study participants [28]. Preliminary data suggest that younger individuals may be at higher risk of experiencing persistent perceptual symptoms in the weeks after taking a serotonergic psychedelic [67]. Though these experiences are often transient and associated with minimal distress or impairment in healthy trial participants [68], they are nonetheless clinically relevant and concerning.

There have been concerns that psychedelic substances may act as triggers for the development of mania or psychosis; this concern has come to predominantly focus on those with genetic predispositions. Though one study of naturalistic psychedelic use among adolescents found support for an association between psychedelic use and manic symptoms, psychedelic use was associated with lower rates of psychotic symptoms when results were adjusted to account for use of other drugs [69]. Given the lack of consensus, careful screening for genetic vulnerability to psychopathology remains important before admitting clients to a PAT program in either research or treatment [34]. The psychedelic medicine to be used must also be carefully considered, with close examination of the most up-to-date research being carried out. Such

rigid standards for research inclusion does, however, mean that results are inherently limited in their generalisability, posing a potential risk for naturalistic use among the general population as well as in cases of poorly informed practitioners or pseudo-practitioners offering psychedelic services.

Risks associated with psychedelic-assisted therapy

In addition to the risks coming from the psychedelics themselves, PAT carries with it all the risks of traditional therapy. From the potential for re-traumatisation to potential worsening as the client unpacks previously ignored material, a PAT therapist must be aware of all the ways in which therapy without psychedelics may cause harm. The risks may be greater in PAT as clients are more vulnerable when under the effect of the psychedelics, making them more pliant to inappropriate therapy and therapist behaviour [70]. One such example involves Health Canada's investigation of the Multidisciplinary Association for Psychedelic Studies (MAPS) when two therapists had their employment terminated after videos from 2015 became public showing the therapists blindfolding, pinning down, and cuddling a participant under the effects of MDMA as part of a clinical trial for the treatment of PTSD; one of the therapists went on to have sex with this participant after the psychedelic treatment while she was still enrolled in the clinical trial [71]. MAPS has since developed a code of ethics for providers administering MDMA-assisted psychotherapy within a MAPS protocol [72]. Although stringent protocols are the norm in psychedelic research, the potential for this form of abuse remains a grave danger. This danger becomes even more concerning in the realm of private practice and in the underground psychedelic treatment scene.

Eating disorder–specific considerations

In addition to these general risks of PAT, there are potential risks that are especially important to consider for individuals living with eating disorders [37]. Dangerously low or high weight may increase the risk for select adverse events. While those of a dangerously low weight may display impaired cardiac, renal, or hepatic function as well as electrolyte imbalance, those with higher weights are more likely to suffer from cardiovascular issues as well as hypertension; both the higher and lower ends of the weight spectrum may lead to complications when using psychedelic medicines [70, 73, 74]. Body weight also poses a potential challenge for dosing, as some psychedelics (such as MDMA) need to be dosed according to weight [75].

Comorbidity also presents a potential obstacle. As previously mentioned, psychedelics are thought to be potential triggers for latent bipolar or psychotic symptoms in those with an existing predisposition; they may also serve to exacerbate existing symptoms [34, 76]. Furthermore, it has been recommended that individuals with personality disorders may require specialist care to benefit from PAT due to difficulty maintaining trust in a therapist and holding a stable therapeutic relationship [27, 77]. As a result, some treat active personality disorders (especially borderline personality disorder) as a contraindication for PAT. Naturally, the presence of multiple comorbidities also represents a more complex case, likely necessitating more extensive psychological preparation before the use of psychedelic medicines.

Medication interactions are yet another potential area of concern for clients struggling with eating disorders. Much clinical research restricts participation to those who are not taking other medications during the PAT intervention; this, of course, does not align with clinical practice, in which many clients will have at least some form of ongoing medication [27, 78]. Careful medical screening is thus of great importance. Particularly worth noting is the potential risk of serotonin syndrome, as eating disorders and many of their comorbid conditions are often treated with medications with serotonergic activity, such as selective serotonin reuptake inhibitors (SSRIs) [79]. Psychedelics such as psilocybin appear to be safe to combine with SSRIs and to have a low risk for serotonin toxicity [80, 81]. However, SSRIs are known to lessen the effects of serotonergic psychedelics, presenting an entirely different form of obstacle [82, 83]. In contrast, MDMA is known to cause serotonin syndrome when combined with some common medications, such as monoamine oxidase inhibitors (MAOIs) [84]. Other common prescription medications may also present an issue, and thus careful matching of the chosen psychedelic medicine to the client is necessary.

Psychedelic medicines may also need to be carefully selected for other reasons. In addition to medical concerns, psychological variables should be kept in mind as well. Some psychedelics may cause nausea and vomiting, but this is especially true of ayahuasca, a traditional South American beverage made from a combination of plants that often includes DMT and various MAOIs [85]. As a result of this purgative effect, this psychedelic medicine may not be appropriate for those whose eating disorders include purging symptomology [27].

There is a lack of research on the effects of psychedelics on younger age groups, which is problematic when one considers the generally early onset of eating disorders. As previously mentioned, younger age may be a risk factor for the development of persisting perceptual symptoms after the use of psychedelics [67]. Nonetheless, some have argued that adolescents should be included in psychedelic research [86]. Without information on the potential long-term effects on development that these substances may cause, however, caution is needed [27].

In addition to the above concerns, some research has suggested psychedelics may increase or decrease appetite, which must be carefully considered for clients with eating disorders [87, 88]. This could potentially worsen disordered eating by increasing restricting or bingeing behaviour during or after psychedelic usage, or improve it if the effects work in the opposite direction of disordered eating symptoms. Such effects are currently not well understood, and hence difficult to predict. Furthermore, PAT involves unique considerations around toilet usage; clients need to be escorted to the washroom and in some cases may soil themselves, requiring cleaning by staff during psychedelic experiences [89, 90]. As people with eating disorders may have complicated relationships with digestion and bodily waste, this area could require special attention.

Ethical considerations

Informed consent, psychoeducation, and ethical-legal guidance

Informed consent refers to the process of sharing as much information as reasonable or prudent individuals would want to know before deciding or consenting to an activity [91]; this includes the likely risks and benefits of treatments, as well as alternatives available. As with the use of psychedelics to treat other mental health concerns [92], clinicians and researchers must navigate several challenges to obtain meaningful informed consent for PAT in people with eating disorders.

One challenge is to accurately communicate the state of current knowledge about the effectiveness of psychedelics. Despite widespread enthusiasm for their therapeutic potential [93], research on the effectiveness of psychedelics in treating eating disorders is still in its early stages, with no known completed randomized clinical trials [94]. As Barber and Dike [95] explained, until conclusive data from rigorous clinical trials are available to demonstrate the safety and efficacy of psychedelics, researchers and clinicians must make every effort to take an unbiased stance in line with the principle of *research equipoise*. It can be difficult to maintain such an attitude in the midst of the current media landscape where the benefits of PAT are often exaggerated [96], possibly leading to unrealistic expectations among potential participants and clients [92].

Another challenge involves helping clients and research participants understand what the treatment will entail, and the wide-ranging possible experiences that they may have, including the possibility for adverse events, as outlined above. Psychedelics induce states of consciousness that have been described as "qualitatively and quantitatively different than those created by most psychotropic medications," which is difficult to convey to someone who has never used these substances [97]. Once begun, it is difficult to abort or reverse a psychedelic experience; as such, the decision to engage in PAT is, for practical purposes, irreversible, precluding the withdrawal of consent [92].

Many clients and trial participants may be naïve to psychedelics, medically unstable, vulnerable, and desperately wishing to alleviate their mental distress [94]. When engaging in the process of informed consent for psychedelic treatment, it is challenging to accurately convey to these individuals the current state of research evidence, the wide range of possible experiences, and the risks of adverse events. For meaningful informed consent that protects the best interests of clients and participants, this task is of critical importance. To address the need for balanced information that can help people make informed decisions, researchers have recommended co-developing information packs with clients who have previously received psychedelic treatment [94]. Additionally, in the face of heterogeneous laws and policies across jurisdictions, there is a need for guidelines and standards to promote best practices for harm reduction and risk mitigation when using psychedelic substances [98]. In some cases, regulations have been altered in ways that are inconsistent with the guidance of professional bodies–for example, MDMA and psilocybin were approved for use in the treatment of depression and PTSD without the support of the Royal Australian & New Zealand College of Psychiatrists [99]. Though conscientious practitioners who follow practice guidelines could theoretically be protected from legal liability [100], conflicting guidance is a major obstacle to bringing the use of psychedelics into a more transparent and legal space.

Economic viability

Described as a "gold rush," there has been immense commercial interest in the potential of psychedelics to treat a wide range of diseases, with nearly 60 companies established to this end [101]. The models of PAT being studied in clinical trials are resource-intensive, and unfortunately, economic analyses have lagged behind clinical research [102]. Though initial cost-effectiveness analyses have suggested that PAT may yield medical cost savings when offered as a treatment for PTSD [103], these analyses were based on placebo-controlled trials, rather than comparisons to existing evidence-based treatments for PTSD. The cost of providing PAT depends on various factors, such as the specific protocol used, the amount of therapeutic contact, and the individual's location. In a recent cost estimate study conducted in California, USA, a group PAT regimen was estimated to cost $3,338, while an individual regimen was estimated to cost $6,804 [104]. With wider implementation beyond clinical trials, the economic feasibility of PAT is uncertain and, if these costs are transferred to clients, they would likely

be prohibitive for many people. It is important that the cost-effectiveness of PAT be considered in light of existing evidence-based treatments for eating disorders. To maximize the accessibility of PAT for people of all socioeconomic strata, research on economic considerations is essential—this includes not only the considerations of pricing and medical cost savings, but importantly, equity and accessibility concerns, as well as safeguards to prevent financial conflicts of interest.

Racial equity in research and treatment

Given the unique clinical presentations of mental health concerns in BIPOC (individuals who are Black, Indigenous, or other peoples of colour, [105]), and known racial and ethnic differences in response to medication [106], the representation of BIPOC in PAT research studies is crucial. Unfortunately, BIPOC are severely underrepresented in this body of research. In a recent review of PAT studies conducted from 2000 to 2017, only 2.5% of participants were African American, 2.1% were of Latino origin, 1.8% were of Asian origin, 4.6% were Indigenous, and 4.6% were of mixed race [107]. These rates are substantially lower compared to the demographic make-up of the U.S., and also compared to the national rates for minority participation in NIH research trials where, for example, African Americans represented 20.6% of participants [107].

Potential explanations for the systemic underrepresentation of BIPOC in psychedelic research include: ineffective recruitment methods, cultural biases inherent in the DSM-5 criteria that may exclude people of colour, the lack of ethnic diversity in the research community, and stigma related to mental disorders and substance use among BIPOC. To maximize the generalizability of research findings and the safety of all participants and clients, greater inclusion of BIPOC in psychedelic research is essential. For a more fulsome discussion of strategies that may help attain this goal, we recommend reviews by Michaels et al. [107] and Morales et al. [108] as well as the application of the EQUIP Health Care approach dimensions of equity-oriented care—cultural safety, harm reduction, trauma and violence-informed care, and contextual tailoring [109].

Extractivism and indigenous inclusion

Another important consideration is who profits from the medicalization and commercialization of psychedelics. In the nascent for-profit psychedelic industry, numerous settler venture capital investors and pharmaceutical companies are profiting from speculative investments, without inclusion of, or benefit to, Indigenous Peoples, the traditional stewards and users of certain psychedelic drugs [110]. As Williams et al. [110] so gracefully put it, "the aptly named 'psychedelic renaissance,' like the European Renaissance, is made possible by colonial extractivism." The clinical promise of PAT owes much of its success to the history of Indigenous healing traditions; though these roots are often acknowledged in clinical trials, few Indigenous people have benefited from such research [111]. To work toward models of psychedelic use that are more equitable for Indigenous Peoples, it is essential that Western medical frameworks broaden to recognize Indigenous ontologies [110] and resist the replication of existing power structures [111].

Methodological considerations

Psychedelic medicines have been used for a long time in some cultures, and there is evidence to support their effectiveness that has been accumulated over generations of observations. It is important to honour the Indigenous knowledge and wisdom that have been passed down through these generations when discussing research on psychedelics. However, it is also important to note that this knowledge has been gathered within a very different context than psychedelic usage in the Western world. Therefore, conducting research in the Western scientific tradition is also necessary, as the ways these substances are used in the Western world are different from their traditional use in other cultures.

One challenge in the psychedelic research field is the predominance of open-label trials and the overstated conclusions drawn from these studies [112]. In early-phase clinical trials, it is common to use open-label designs (those lacking a control arm) with small sample sizes and short-term follow up. This rudimentary study design can establish preliminary evidence of safety and treatment effect prior to embarking on larger, double-blinded, randomized controlled trials (RCTs). Although these preliminary studies make important contributions to knowledge about PAT, the conclusions drawn from them are sometimes overstated. van Elk and Fried [112] provide an example of an open-label study that enrolled 27 psilocybin-treated participants with major depressive disorder (MDD; [113]). After one year, about 60% of the participants were no longer depressed, and the authors concluded that there were "substantial effects of psilocybin-assisted therapy." While the study's results are promising, without a control arm, the improvement in depressive symptoms cannot be attributed to psilocybin. Due to factors such as placebo response, regression to the mean, and spontaneous remission, as many as 53% of participants in MDD trials will recover *without*

treatment after one year [114]. Furthermore, effect sizes from underpowered studies tend to be inflated, thereby further compounding the problem of prematurely drawing conclusions from open-label trials. Another issue concerns the rigid inclusion criteria: participants in PAT clinical trials are often required to have no comorbid mental disorders or substance use concerns, and must screen negative for personal and family history of schizophrenia, bipolar, or psychotic disorders, as well as previous psychedelic use [115]. These rigid exclusion criteria may limit the generalizability of findings to the wider population.

Possibly due to the over-reporting of effects from small studies and the sensational nature of some psychedelic research, popular media outlets have perpetuated the premature narrative that psychedelics are an effective treatment for psychiatric illnesses [116]. An unintended consequence of this overzealous reporting is that psychedelic clinical trial participants who have internalized this narrative may have high levels of positive expectancy, which is a known factor that can enhance placebo response [112]. To further compound the problem of strong placebo response due to positive expectancy, RCTs in psychedelic research are plagued by the problem of 'unblinding.' Due to the pronounced and distinctive psychological and physiological effects of psychedelics (e.g., perceptual distortions), it is challenging to find an 'active' placebo that will, at least to some degree, mimic the effects of psychedelics. Thus, without known exceptions, participants in the psychedelic arms of clinical trials are unblinded, meaning they are aware of their arm assignment, either from the beginning or by the end of the study [117]. As a result, positive expectancy may then account for symptom improvement rather than psychedelics themselves. Moreover, control arm participants being unblinded can lead to pronounced nocebo effects (i.e., exaggerated negative response to the placebo) and higher levels of study dropout in the placebo arm, representing another threat to internal validity. Thus, when considered together, the psychedelic arm may have inflated positive effects, and conversely, the placebo arm may have enhanced negative effects, thereby leading to an overestimated between-group effect size. Notably, few RCTs examining PAT assess and report on whether adequate blinding was maintained [118]. A review of randomized clinical trials of PAT found considerable risk of bias among the included studies, mainly due to a lack of adherence to the intended interventions, as well as issues with outcome measurement and blinding [117]. Importantly, out of the seven included studies that reported on the success of blinding, none found it to be successful for either the clients or the study personnel. Without adequate blinding, the internal validity of psychedelic research results is critically compromised.

Double-blinded, adequately-powered RCTs are the gold standard for the evaluation of new drug treatments [119]; accordingly, they represent a critical step in order for the field to move forward. There is increasing recognition, however, that RCTs often do not represent the most efficient design, and they can be complex to apply when examining PAT. Adaptive design trials are a flexible alternative, allowing trial modifications to be made while maintaining validity and integrity, and enabling researchers to examine heterogeneity in participant responses [120]. To address the challenge of successful blinding and reduce the risk of bias, other recommended strategies include: the use of parallel-group designs and active placebos (e.g., a low dose of the psychedelic used in the active treatment condition), recruitment of psychedelic-naïve participants, pre-registration and protocol publication, evaluation of blinding, and measurement of expectancy and therapeutic fidelity [117]. Regarding the evaluation of outcomes, it is important not only that ratings be blinded, but that the results of this blinding be reported transparently. Outcome measures should be carefully selected. In addition to symptom-focused outcome measures, subjective psychedelic experiences of participants should be assessed using a validated measure [121], as these experiences may predict the effectiveness of PAT [122].

Spill the T: Centering psychotherapy in PAT

Although a great deal of attention has been given to ensuring the safe administration of psychedelics in PAT trials, less focus appears to have been placed on the psychotherapeutic interventions themselves. Therapy protocols are often underreported and lacking transparency, making it difficult to determine or replicate the specifics of the interventions used. A systematic review of PAT identified 55 papers reporting on 26 studies [123]. An additional 45 papers were identified that described the results of PAT *without* describing the specific psychological interventions used [123]– in other words, nearly half of the studies on PAT identified in this review, did not provide adequate descriptions of the therapy they employed. The papers that described psychological interventions described 11 different approaches, including both ad-hoc therapeutic models (i.e., purpose-built approaches devised for use in PAT) and adapted models (i.e., evidence-based therapies developed in other settings

and later adopted for PAT, such as cognitive-behavioural therapy adaptations). Although there was great variability in the approaches used and the level of detail they were described in, almost all adapted and ad-hoc therapeutic models included: a preparation phase, where sessions focused on the establishment of therapeutic alliance and discussing aims and intentions; a drug sessions phase, where therapeutic interactions aimed to guide participant attention and provide support during challenging moments; and an integration phase where, as the substance's effects subside, clients are encouraged to process their experience and consider its relevance to their everyday life [123].

Therapeutic interventions in PAT tend to involve supportive conversations that follow the client's lead and encourage insight into psychological problems, rather than symptom-focused interventions. In contrast, in the treatment of eating disorders, the most effective psychological therapies involve highly structured, manualized, behaviour-centered session-by-session protocols designed to normalize eating as quickly as possible and address underlying risk and maintenance factors. For adults, Cognitive Behaviour Therapy – Enhanced (CBT-E) is one of the approaches with the most evidence showing the greatest impact on symptom reduction and other outcomes; CBT-E is typically delivered in 20 sessions for bulimia nervosa and binge eating disorder, and in 40 sessions for anorexia nervosa [124]. Briefer forms of CBT have also been developed, with accumulating evidence demonstrating their effectiveness [125]. These evidence-based eating disorder interventions are typically delivered by care providers trained specifically in eating disorder treatment.

No known trials have yet paired specialized, evidence-based eating disorder interventions with psychedelic drug administration; as such, it is unclear whether these therapies would be effective in combination, let alone compatible. Given the structured, manualized nature of effective eating disorder treatments, adaptations of these protocols for use in PAT will require careful consideration of logistical factors, time constraints, and therapeutic goals. Key considerations include ensuring the therapy remains structured and tailored to the complexities of eating disorders, while addressing symptoms *and* allowing for the introspective benefits facilitated by psychedelics. Additionally, thorough reporting and transparency in therapy protocols are essential to ensure replicability and rigor in clinical trials. As psychological interventions are developed and adapted for use in PAT for eating disorders, fidelity assessments should be incorporated to ensure these approaches are implemented consistently. Examining the impact of specific interventions [126], subjective psychedelic experiences [121], as well as of the general factors of psychotherapy (e.g., the therapeutic alliance) [127], will also help identify potential mechanisms and critical components of effective PAT for eating disorders.

Conclusions

In examining the issues listed above, it becomes clear that though excitement for PAT is warranted, so too is caution. Further clinical trials of PAT for eating disorders are needed for us to see what the outcomes of this line of inquiry will be. We offer a condensed list of our provisional guidelines for clinical research (Table 1) that outlines some important issues—and their potential solutions—that must be taken into account in designing both clinical trials and treatment protocols. In addition to this, we also highly recommend a recent paper by van Elk and Fried [112] that provides a more in-depth overview of some issues and solutions in the realm of psychedelic science broadly, as well as a paper on safety considerations [37]. We hope that by addressing potential issues, future research into using PAT for treating eating disorders will be improved, maintaining a high standard of safety and sound experimental design.

Table 1 Provisional guidelines for clinical research trials

Issue	Recommendation
Risks associated with screening (e.g., overlooking comorbidities, selecting a psychedelic incompatible with participant's existing medications)	Careful interdisciplinary screening with a psychiatrist/MD, pharmacist, and psychologist. Develop guidelines for screening participants in psychedelic-assisted therapy trials.
Informed consent is challenging to obtain, especially from those without past experiences with psychedelics	Accurately convey current research evidence, alternative treatment options, and the wide range of possible experiences and outcomes, as well as the risks of adverse events. Co-develop information packages and consent materials with people who have received PAT.
Risk for adverse effects	Thorough informed consent process; exclude participants with personal or familial history of bipolar or psychotic disorders; ensure sufficient psychological preparation before treatment; ensure appropriate medical equipment and personnel, including therapeutic supports before, after, and during drug administration; rigorous monitoring and reporting of adverse events. Practitioners should have appropriate training and supervision in psychedelic-assisted therapy as well as eating disorder treatment; development and implementation of stringent safety standards and protocols.
Developmental concerns for younger age groups	Extreme caution for younger age groups until more research demonstrates absence of harm.
Studies with no control group, small sample sizes, and short study duration have limited internal validity.	Larger, double-blinded, randomized control trials of psychedelic-assisted eating disorder treatment; include control groups, achieve adequate power, and have longer term follow-up (> 12 months). Adaptive trial designs represent a flexible alternative. Team science/multi-center collaborations can mitigate costs (van Elk and Fried, 2023). If further open-label studies are conducted, researchers should interpret data cautiously and clearly explain design limitations.
Placebo effect secondary to positive expectancy. 'Unblinding' (of participants and researchers) due to obvious psychoactive effects of psychedelics.	Include measures of expectancy and social desirability, and control for these variables. Manage participant expectations prior to study commencement (e.g., adding explicit information in consent forms about the uncertainty of psychedelics' positive effects). Blinding can be enhanced by using 'active' placebos (e.g., psychostimulant, diphenhydramine, low dose psychedelics, and/or antidepressants). Recruit psychedelic-naïve participants because they will have less awareness of the psychedelic effect, and hence, will be more likely to be 'blinded' to group assignment. Assess and report on success of blinding of both participants and researchers.
Uncertain economic viability	Further research on cost effectiveness, with attention to equity and accessibility; safeguards to prevent financial conflicts of interest.
Racial inequity and extractivism	Greater inclusion of BIPOC in psychedelic research, not only as participants, but community partners to guide research and decision-making.
Insufficient focus on psychotherapy interventions used in PAT	Adaptations of existing evidence-based eating disorder treatment approaches; thorough reporting and transparency in therapy protocols; incorporating fidelity assessments; examining impact of specific interventions, subjective psychedelic experiences, and general factors of psychotherapy.

Abbreviations

LSD	Lysergic acid diethylamide
DMT	N, N-dimethyltryptamine
MDMA	3,4-methylenedioxy-methamphetamine
NMDA	N-methyl-D-asparate
PAT	Psychedelic-assisted therapies
PTSD	Post-traumatic stress disorder
MAPS	Multidisciplinary Association for Psychedelic Studies
SSRIs	Selective serotonin reuptake inhibitors
MDD	Major depressive disorder
RCT	Randomized controlled trial

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ST and PH are Editors in Chief of the Journal of Eating Disorders. ST receives royalties from Taylor and Francis, Hogrefe and Huber and McGraw Hill for published book chapters. He has received honoraria from Shire/ Takeda Group of Companies for chairing the Australian Clinical Advisory Board for Binge Eating Disorder, public speaking engagements, commissioned reports as well as investigator-initiated research grants. He is an inaugural committee member of the National Eating Disorders Collaboration, a Member of the Technical Advisory Group (TAG) on Eating Disorders (Commonwealth of Australia) and a member of the governing council of the Australian Eating Disorders Research and Translation Centre. PH has received sessional fees from the Therapeutic Guidelines publication and the Health Education and Training Institute (HETI, NSW), and royalties/honoraria from Hogrefe and Huber, McGraw Hill Education, Blackwell Scientific Publications, BioMed Central, and PLOS Medicine. She is a consultant to Tryptamine Therapeutics, has prepared a report under contract for Takeda (formerly Shire) Pharmaceuticals regarding binge eating disorder (July 2017), and has been a consultant to Takeda Pharmaceuticals. EL currently holds research support in the form of a Harrison McCain Young Scholars Award and has been an independent consultant to the Power Within project (a collaboration with the Dove Self-Esteem Project, Plan International Canada, and Women and Gender Equality Canada).

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