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What should constitute a control condition in psychedelic drug trials?

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Over the past decade there has been a surge in interest in placebo-controlled trials using non-classical 3,4-methylenedioxymethamphetamine (MDMA) and classical psychedelics such as psilocybin, lysergic acid diethylamide (LSD) and *N*,*N*-dimethyltryptamine (DMT) to treat neuropsychiatric disorders. However, the success and reliability of these trials depend on the design of the trials, the choice of control conditions, and the ability to blind both participants and researchers. When appropriate control conditions are lacking, it becomes difficult to disentangle placebo and expectation effects from medication effects. Here we explore the neurobiology of placebo and expectation effects, alongside the methodological considerations for selecting suitable control conditions in psychedelic trials. This includes examining the advantages and disadvantages of various control conditions and proposing new directions to enhance the validity of these trials and their regulatory science. By addressing these factors, we aim to improve the reliability of psychedelic research in uncovering the therapeutic benefits of psychedelics beyond placebo and expectation effects.

Recently, psychedelics have gained attention as potential treatments for 'all sorts of health issues'[1], including post-traumatic stress disorder (PTSD)[2,3], depression[4,5] and untreatable pain[6,7]. The term 'psychedelics' traditionally refers to substances that primarily exert their effects through agonism at serotonin 5-HT2A receptors, and these include psilocybin, lysergic acid diethylamide (LSD) and *N*,*N*-dimethyltryptamine (DMT; a component of the ayahuasca brew). These substances are considered classical serotonergic psychedelics due to their shared pharmacological mechanism. More broadly, the term 'rapid acting therapeutics' refers to a novel category of therapeutic compounds known for their ability to induce both rapid and sustained plastogenic changes in structural plasticity and behavior following single administrations[8]. This class includes a range of substances, including the serotonergic psychedelics, but also 3,4-methylenedioxymethamphetamine (MDMA)—a synthetic amphetamine derivative known for its entactogenic properties—and ketamine, as well as other glutamatergic modulators, despite their distinct primary pharmacological targets[8]. Non-classical psychedelic MDMA primarily acts through serotonin release and reuptake inhibition[9], whereas ketamine acts through *N*-methyl-D-aspartate receptor antagonism[10] and mu opioid receptor binding[11], and the (2*R*,6*R*)-HNK enantiomer involves early and sustained activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors[12–14]. All these substances share commonalities in their potential to induce altered states of consciousness and rapid therapeutic benefits, so we include them in this exploration of placebo effects, expectations and trial methodologies (Box 1).

The number of Investigational New Drug applications for psychedelics has also undergone an exponential increase, accompanied by substantial venture investment in the field. Two phase 3 trials have demonstrated potential beneficial effects of MDMA-integrated assisted psychotherapy for PTSD[3,15,16], leading to an Investigational New Drug submission to the US Food Drug Administration (FDA) for an investigational MDMA-assisted therapy for individuals with PTSD. The FDA has previously acknowledged the therapeutic potential of MDMA, granting a priority review to a new drug application by Lykos Therapeutics for drugs that could substantially enhance the treatment, diagnosis or prevention of serious conditions compared to standard methods[2,17,18]. However, an FDA advisory panel voted against approving MDMA-assisted therapy for PTSD[19]. Following a meeting on 4 June 2024, FDA advisors voted 9 to 2 that the available data did not

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BOX 1

Definitions

- **Active placebo**: a placebo that mimics some side effects or sensations of the active treatment to maintain blinding in clinical trials.
- **Blinding (masking)**: a method used in clinical trials to prevent bias by ensuring that participants and/or researchers do not know whether a participant is receiving the active treatment or a placebo.
- **Expectation effect**: the influence of patient expectations about treatment outcomes on their actual response to the treatment, which can substantially impact therapeutic efficacy.
- **Expectation management**: process of aligning the expectations of patients, caregivers and healthcare providers about treatment outcomes, procedures, recovery timelines and overall care.
- **Extended reality**: a digital technology that combines virtual reality and augmented reality to simulate immersive environments.
- **Placebo effect**: the phenomenon in which a patient experiences a perceived improvement in their condition due to the belief that they are receiving an active treatment, despite actually receiving an inactive substance (placebo).
- **Psychedelics**: substances such as psilocybin, LSD and DMT that primarily act through agonism at serotonin 5-HT2A receptors, known for inducing altered states of consciousness and therapeutic benefits.
- **Nocebo effect**: the opposite of the placebo effect, in which negative expectations about a treatment lead to adverse effects or worsening of symptoms.
- **Rapid acting therapeutics**: a class of fast-acting therapeutics that rapidly promote structural and functional neural plasticity; rapid acting plastogenic compounds include psychedelics, ketamine and, potentially, MDMA.

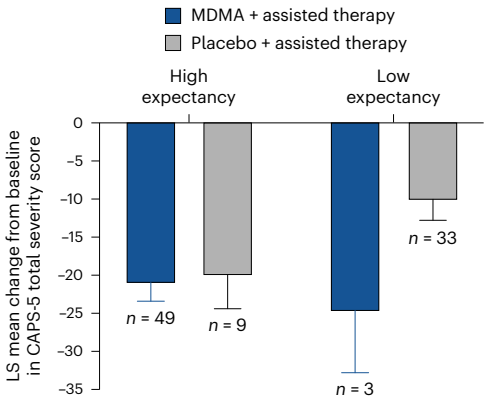

Fig. 1 | Preliminary evaluation of expectation of benefit in a phase 3 trial of MDMA plus assisted therapy versus placebo plus assisted therapy in participants with moderate to severe PTSD. Presented is LS mean change in the clinician-administered PTSD scale for DSM-5 (CAPS-5) total severity score. Data are redrawn from a slide presented by a statistical consultant to Lykos at the FDA meeting hosted on 4 June 2024. LS, least squares. Source: https://psychedelicalpha.com/news/live-coverage-fda-advisory-committee-reviews-mdma-assisted-therapy-for-ptsd.

demonstrate MDMA's efficacy in treating PTSD, and 10 to 1 that the benefits of MDMA-assisted therapy did not outweigh the risks. This decision has brought the field under scrutiny, raising concerns about the validity of the research and the safety of trial participants.

The panel highlighted methodological issues, such as the blinding of the study—most patients correctly identified that they had been given MDMA—and 'very strong prior beliefs' about the benefits of the treatment among both participants and therapists, which 'raise concerns about bias'[20], including expectation effects (Fig. 1). Additionally, concerns were raised about not reporting side effects and study participants being pressured to hide such adverse effects.

MDMA has been used by mental health professionals alongside talk therapy since the 1970s, with the goal of helping patients to better access, process and express challenging emotions and experiences[18,21,22]. Concerns about the validity of the results reiterate a need for rigorous research along with measures to ensure safety.

In this Review we discuss the state of the art of placebo and expectation effects, the current use of control conditions and dose–response curves in psychedelic trials, the need for measurements of expectations, and the potential for alternate blinding ways to better manage expectations. The goal is to establish methodologies that ensure the reliability and generalizability of findings, the safety and rigor of psychedelic therapeutics, disentangling the placebo response from the intrinsic action of drugs at the level of the central nervous system, and understanding the challenges and opportunities in the evolving psychedelic field.

Placebo and nocebo effects

Placebo and nocebo effects stem from patients' positive and negative expectations about their health, respectively[23]. At the neurobiological level, placebo analgesic effects seem to involve the release of substances such as endogenous opioids and can be antagonized by the opioid antagonist naloxone[24,25]. Other systems are involved in placebo effects in conditions other than pain[26]. Conversely, the enhancement of pain, known as a nocebo effect, is probably mediated by the neuropeptide cholecystokinin. This effect can be inhibited by proglumide, which acts as a mixed cholecystokinin type-A/B receptor antagonist[27,28]. Additionally, nocebo-induced hyperalgesia is associated with increased activity of the hypothalamic–pituitary–adrenal axis, resulting in elevated levels of adrenocorticotropic hormone and cortisol in the plasma[28]. This knowledge of the neurobiology of placebo and nocebo effects stems mainly from well-controlled laboratory research studies. However, little well-controlled laboratory research has been conducted in the arena of psychedelics. One study investigated whether placebo alone can induce psychedelic-like experiences in a naturalistic setting resembling a psychedelic party[29]. Thirty-three students participated in a single-arm study where they consumed a placebo described as resembling psilocybin, accompanied by a setting designed to enhance expectations of a psychedelic experience. Despite the absence of any actual psychedelic substances, many participants reported substantial alterations in consciousness. The authors provided normative data on the effects of various psilocybin doses for reference 30. The vast majority of changes in the 5-dimensional altered states of consciousness rating scale were below the 'low' range (120 μg kg^{-1}). These placebo effects varied widely among individuals, with 61% verbally reporting some form of perceptual or sensory changes. The findings underscore the role of context and expectations in producing psychedelic-like effects and highlight the importance of these factors in both research design and therapeutic practice[29].

Similar effects can manifest in various clinical scenarios, such as reactions to an active agent in routine practice or a placebo in a clinical trial[31], during the informed consent process[32], when conveying information about medical treatments, and through public health campaigns[33,34]. The variability in patients' treatment responses and symptom experiences can also be partly explained by placebo and nocebo effects (better defined in laboratory settings) and placebo and nocebo responses (in randomized clinical trials)[35–38]. In randomized clinical trials, responses to placebo in the treatment of pain[39] or

psychiatric disorders[40] are often comparable to those seen with active treatments. In terms of nocebo responses, up to 19% of adults and 26% of the elderly report side effects from placebos[41]. Furthermore, as many as 25% of patients given a placebo in clinical trials discontinue its use due to adverse effects, indicating that nocebo effects may contribute to treatment discontinuation and poor adherence to active therapies[42,43].

Placebo (and nocebo) responses are influenced by factors such as the nature of the illness, biases, co-interventions and the characteristics of the treatment itself[34,44,45]. Psychedelic trials are known to exhibit high placebo responses, including spontaneous improvements due to natural disease fluctuations, making it challenging to demonstrate efficacy in the absence of adequate controls and comparators.

Treatment expectations and clinical outcomes

Expectations of treatment benefits may amplify the effects of any treatments. Expectations, which are beliefs about treatment outcomes, have been shown to be strongly associated with improvements. High treatment expectations improve the effects of morphine, diazepam, deep brain stimulation[26], remifentanil[46], lidocaine[47] acupuncture[48] and surgery[49].

In the field of pain, treatment expectations are considered one of the dominant mechanisms behind endogenous pain modulation. These expectations can be influenced by previous therapeutic experiences (for example, conditioning), verbal suggestions and social observations. A large study involving 2,722 participants with chronic pain provided strong evidence for the predictive relationship between treatment expectations and outcomes[50]. Participants were recruited from three multidisciplinary pain treatment centers, and their expectations of pain relief over the next six months were measured at baseline using a visual analogue scale (VAS) ranging from 0 ('no relief') to 100 ('complete relief'). The results indicated that higher baseline expectations of pain relief predicted larger reductions in chronic pain intensity and depressive symptoms, with expectations accounting for ~23% of the variance in chronic pain intensities[50].

A recent meta-analysis of nine studies involving 436 participants demonstrated a significant reduction in depression scores with psilocybin compared with other treatments, including placebo, niacin and microdoses (Hedges' $g = 1.64$, 95% confidence interval 0.55–2.73, $P < 0.001$)[51]. Psilocybin treatment had larger effects in individuals with secondary depression (that is, depression that develops in someone already dealing with another psychiatric disorder or a serious medical illness, such as end of life due to cancer), when assessed using self-report depression scales, and among older participants and those with previous experience with psychedelics. This meta-analysis appeared to miscalculate and significantly overstate the effect size. Moreover, those with a history of psychedelic use had a more pronounced effect of psilocybin[51], suggesting that prior use of psychedelics may create an expectancy bias with a boosting effect on psilocybin, further emphasizing the relevance of investigating expectancy in the context of psychedelics and other antidepressants.

Using educational scripts to set realistic treatment expectations can reduce placebo responses. One study evaluated the placebo-control reminder script (PCRS), a brief interactive procedure that educates participants about placebo effects. Participants with major depressive or psychotic disorders and moderate depression were informed they had a 50% chance of receiving an experimental antidepressant or a placebo, although all received a placebo. Those who received the PCRS ($n = 70$) showed smaller reductions in depression scores (lower placebo response) compared to those who did not receive the PCRS ($n = 67$). The PCRS group also reported fewer adverse events (nocebo effect). Educating participants about placebo responses can reduce high placebo rates. Using scripts to set realistic expectations and temper hype in psychedelic trials could improve participant outcomes and study validity.

Small-study effects and replicability

Many clinical research studies, ranging from 60% to 90%, are not successfully replicated[52]. A recent meta-analysis across scientific disciplines identified common biases contributing to this issue, such as small-study effects, publication bias and citation bias[53]. Small-study effects, where smaller studies tend to report larger effect sizes, are particularly problematic. Ignoring placebo responses and effects can also lead to failures in replicating study results. Regression to the mean, natural history, quality of blinding, and placebo effects result in lack of reproducibility, such that promising results from phase 2 trials do not replicate in phase 3 trials[54]. In fact, 55% of phase 3 trials fail due to lack of efficacy, despite positive results in the earlier phase[55]. These aspects apply to current trials with psychedelics, which often have a small sample size, are characterized by poor quality of blinding and assisted therapy, therefore leading to potentially large placebo effects.

Inert placebo versus active placebo versus open-label placebo

The traditional method to establish effectiveness assumes additivity[56]. Additivity refers to the summation of placebo and active treatment effects. The problem of the assumption of additivity is that it does not take into account the fact that the higher the placebo response rate, the smaller the effect size, as demonstrated by a large meta-analysis of trials of FDA-approved antidepressants[57]. The psychedelic overall effect is derived by subtracting the placebo group's effect from the active treatment group's effect[56]. Both inert and active placebos have been used (Table 1).

The use of real placebos, inactive by nature, has been criticized by some as not providing adequate control[58]. The use of inert placebos in psychedelic trials aims to treat these trials in the same way as the trials with inert placebos for other psychotropic compounds with very distinctive (and therefore potentially unblinding) side-effect profiles (for example, esketamine or quetiapine)[59,60]. However, the drawback of the inert placebos with psychedelics is a substantial risk of unblinding compared to the use of active placebos[61]. In line with this, Soliman and colleagues conducted a meta-analysis to investigate aspects such as (1) placebo selection, (2) study design and (3) blinding integrity in non-classical psychedelics (for example, MDMA) and the classical psychedelics (for example, psilocybin, LSD and DMT used in assisted therapy for psychiatric disorders[61]. Sixteen publications met the criteria for review, and the results indicate that inert placebos may be insufficient to control expectancy effects. The authors suggested that reducing personnel unblinding and using active placebos may be crucial for future clinical studies involving psychedelics[61]. The limitation of this meta-analysis is its focus on psychedelics administered with assisted therapy, which may introduce bias and unblinding. It is unclear whether unblinding with psychedelics alone (without assisted therapy) is greater than unblinding with drugs such as esketamine or quetiapine. Additionally, Olson and colleagues found that a placebo disguised as a psychedelic caused many participants to report considerable changes in consciousness, similar to low doses of psilocybin[29].

Active placebos that induce psychoactive effects include niacin[62,63], ethanol[64], midazolam[65] and diphenhydramine[66], among others. The adoption of an active placebo typically induces some side effects that may in part mimic the experience of psychedelic treatments. The disadvantage of this approach is that it provides an underestimate of the safety of the psychedelic compound, as the frequency of side events in the active placebo arm is not negligible. Also, midazolam, when used as an active placebo, did not mask the dissociative symptoms observed at higher doses of ketamine[65]. Another disadvantage of this approach is that patients' expectations may be greater and therefore reduce the difference in drug versus placebo responses.

However, active placebos reduce the risk that patients and clinical researchers can distinguish the active treatment from the placebo, thus minimizing the risk of bias due to unblinding in psychedelic trials[67].

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Table 1 | Pros and cons in psychedelic trials for inert placebo, active placebo, open-label placebo, dose-ranging strategy and expectation assessment

Approach	Pros	Cons
Inert placebo	Provides a clear control for efficacy comparison	Greater risk of unblinding due to lack of psychoactive effects, although not dissimilar from trials with drugs such as esketamine and quetiapine
	Mimics traditional placebo controls used in other psychotropic trials	Potentially inadequate control of expectancy effects
	Accurate assessment of safety	Greater potential for bias and placebo response in psychedelic trials
Active placebo	Reduces the risk of unblinding by mimicking some side effects	May underestimate the safety of the psychedelic compound due to induced side effects
	Provides a better control for expectancy effects	Patients' expectations may be higher, reducing the observable difference between drug and placebo responses
		Some active placebos may not adequately mask all psychedelic effects
Open-label placebo	Enhances transparency and ethical standards	Participants may drop out sooner due to knowing they are receiving a placebo
	Can contribute to more authentic therapeutic relationships	Different expectations may influence outcomes, limiting generalizability
	Allows the study of psychological and contextual factors	Potentially higher variability in reported outcomes
Dose-ranging strategy	Uses low, middle and high doses to minimize unblinding	Higher expectations across all doses may increase placebo responses
	Participants informed they will learn their actual dose post-study	Uniformly high expectations may lead to underestimation of treatment efficacy
		Efficacy of lower doses depends on perceived effectiveness
Measurement of expectations	Allows for adjustment of treatment strategies on the basis of evolving expectations during the trial	Use of validated scales (for example, the Stanford Expectations of Treatment Scale, the Treatment Expectation Questionnaire and so on) may require additional resources and time
	VAS captures nuance of shifts in beliefs that can enhance clinical benefits and are easy to implement.	

Different considerations can be made in contexts other than psychedelic medicine. For example, a Cochrane review evaluating an active placebo versus standard placebo intervention in 21 randomized clinical trials with 1,462 participants showed no statistically significant differences between active and standard placebo controls[68].

An open-label placebo is a treatment approach where patients are fully aware that they are receiving a placebo, devoid of any active therapeutic ingredients[69–72]. Unlike traditional placebos administered covertly, open-label placebo involves transparent communication with participants regarding the inert nature of the treatment[73,74]. Combining conditioning with open-label placebos in the immediate postoperative period reduced daily opioid use by ~30% and lowered daily worst pain scores among spine surgery patients compared to treatment as usual, although no significant difference was found in average daily pain[75].

In the context of psychedelic trials, where the therapeutic alliance is crucial, open-label placebos may contribute to more authentic therapeutic relationships. Open-label placebo trials may identify psychological and contextual factors influencing clinical outcomes. However, participants in the open-label placebo arm may drop out sooner, have different expectations compared to those in traditional blinded studies, potentially influencing reported outcomes and limiting the generalizability of the findings. Understanding these factors is crucial for interpreting clinical outcomes in psychedelic research.

Regardless of the controls adopted, the use of independent, remote raters or self-rated assessments is needed. In an era of technological advancements, using remote grading, such as ecological momentary assessments[76], brings a new dimension to trial evaluation by offering self-evaluation, reducing clinician biases, and addressing challenges related to in-person assessments. However, ecological momentary assessments can be considered highly burdensome by some patients and may contribute to substantial attrition and incomplete follow-up assessments, although the reliability and acceptance of remote grading in psychedelic drug trials has the advantage of minimizing the impact of non-pharmacological aspects of the treatment, while ensuring careful monitoring for safety matters. Implementing measures such as risk evaluation and mitigation strategies[77], comprehensive training programs and oversight by state boards can address potential biases and ensure the safety of study participants.

Dose-ranging strategy

The dose-ranging strategy uses low, middle and high doses in parallel arms. This approach minimizes unblinding by randomizing participants to different doses with the assumption that even a low dose can elicit some psychedelic side effects. An authorized concealment of the dose could be in place[78–81]. Participants are typically told that they receive one of the three doses, and that at the end of the study they will be informed about the actual dose they were administered. By authorizing the concealment during the consent form, transparency and autonomy to participate (or not participate) in the study are preserved. A debriefing follows along with the opportunity to receive the therapeutic dose (Table 1).

A trial adopting this approach, such as the psilocybin trial in treatment-resistant depression[5], has not fully assessed the degree of the psychedelic experience, and therefore the relationship with clinical outcomes. A drawback of this approach is that, if middle and high doses are considered by participants to be effective, this can lead to a greater placebo response, as indicated by a meta-analysis showing that the presence of two active arms in a placebo-controlled trial leads to higher placebo responses than when there is only one active arm[82].

Moreover, in dose-ranging trials, the appropriateness of lower doses depends on perceptions of effectiveness by clinicians and patients. For instance, a ketamine trial found robust improvement

in depressive symptoms at 0.1 mg kg^{-1}, comparable to 0.5 mg kg^{-1}, suggesting efficacy at lower doses (0.1 mg kg^{-1} versus 0.5 mg kg^{-1})[65]. Conversely, biases toward underestimating improvement with lower doses may occur if attenuated adverse events are seen as indicative of ineffectiveness, as seen in a psilocybin trial where a 1-mg dose showed less reduction in depression scores compared to higher doses[5]. A 25-mg dose significantly reduced depression scores more than the 1-mg dose over three weeks, with a mean Montgomery–Asberg depression rating scale (MADRS) score change of −12.0 compared to −5.4 ($P < 0.001$). Adverse events, including headache, nausea and dizziness, occurred in 77% of participants, with suicidal ideation or behavior reported across all dose groups. Unexpectedly, the 1-mg low psilocybin dose induced a nine-point reduction in the MADRS score, which is lower than the change in MADRS score on day 2 in the ayahuasca trial, which used inert placebo as a comparator[83]. However, the placebo in this trial had features (taste and color) similar to ayahuasca. This may have led some participants to believe that they had taken ayahuasca, resulting in a larger therapeutic effect in the ayahuasca trial[83] than in the psilocybin trial[5].

Therefore, by virtue of telling participants that they all receive the psychedelic drug (even though in different doses), expectations of benefits are equally high across arms. Participants will learn their actual dose after the study. This preserves transparency and autonomy. However, if middle and high doses are perceived as effective, it may increase placebo responses. The efficacy of lower doses also depends on their perceived effectiveness. This approach could lead to an underestimation of treatment efficacy due to uniformly high expectations of benefit.

Measurement of expectations as a normative practice

Expectations substantially shape medical conditions, influencing outcomes such as long-term mortality and surgical results[23]. Depressed individuals lack the typical optimism bias, but positive belief shifts following ketamine treatment have shown clinical benefits[84].

Recently, Szigeti and colleagues reported on a pretreatment expectation measurement in relation to the outcome of a psilocybin versus escitalopram study[85]. Patients exhibited much higher expectations for psilocybin than for escitalopram[86]. Despite this, the expectation for escitalopram correlated with better therapeutic outcomes, whereas the expectation for psilocybin did not predict its therapeutic response[86]. This study is limited by measuring expectations only once before the treatment and by using a small sample size ($n = 55$).

The impact of new beliefs, especially those reinforced during preparatory sessions, suggests prolonged clinical benefits. Colloca and colleagues[87] advocated for integrating longitudinal expectation assessments in patients and clinicians to enhance the interpretation of clinical trial findings and optimize treatment approaches in clinical settings. By measuring and controlling for dynamic changes in participants' expectations, we can gain insights into the interplay of expectations with psychedelics and MDMA. In this regard, media hype can affect pretreatment expectations and complicate treatment evaluations.

Expectations of psychedelic-related benefits should be measured before, during and after treatment. It is possible to use validated existing scales, such as the Stanford Expectations of Treatment Scale[88], the Treatment Expectation Questionnaire[89,90] or simply a VAS[91] that captures the nuances of the anticipated symptoms (for example, euphoria, well-being, desire of improvement) by anchoring the question to a range of 0 = no improvement to 100 = maximum improvement. In a recent study, expectations of pain relief from treatment over six months were measured at baseline, using a VAS ranging from 0 = no relief to 100 = complete relief[50]. The results showed that higher levels of pain relief expectations at baseline predict larger reductions in chronic pain intensity and depressive symptoms[50], with expectations accounting for ~23% of the variance in chronic pain intensity outcomes[50].

Table 2 | Recommendations for psychedelic trials

Component	Recommendation
Trial design	To minimize unblinding and optimize the separation of expectation versus drug effects, consider a 2×2 factorial design with authorized deception, naive participants and microdoses. Alternately, use an SPCD to control placebo responses by re-randomizing non-responders. An overt–covert design, administering treatment without knowledge of timing, could minimize bias. Use of anesthesia ensures blinding by silencing expectations. Finally, XR offers a controlled, drug-free psychedelic experience through VR.
Safety monitoring	Implement risk evaluation and mitigation strategies, comprehensive training programs and oversight by state boards to ensure safety and address potential biases in psychedelic drug trials.
Participant education	Use educational scripts to set realistic treatment expectations and reduce placebo responses. Scripts such as the PCRS can educate participants about placebo effects and improve study validity.
Pretreatment preparation	Conduct structured in-person sessions and follow-up calls to build constructive expectations about psychedelic therapy. Include guided visualizations and discussions about treatment mechanisms and potential benefits.
Dynamic assessment of expectations	Integrate regular assessments of treatment expectations by both patients and clinicians throughout the trial process. Use standardized scales and protocols to capture changes in expectations over time and ensure alignment with treatment outcomes. This can contribute to more nuanced interpretation of trial outcomes and better management of placebo responses.

In the context of placebo effects, treatment expectations are one of the main mechanisms in the formation of these effects[92–96]. Expectations of symptom relief can be modified by previous therapeutic experiences (for example, having used psychedelics), verbal suggestions of improvements, and social communication and observations of improvements in others[92].

Before the psychedelic experience, participants could engage in structured in-person sessions and follow-up calls focused on building constructive expectations about the treatment in psychedelic medicine[87]. These sessions might include guided visualizations of the therapeutic process and comprehensive discussions about the mechanisms and potential benefits of psychedelic therapy to improve participant outcomes and the reliability of psychedelic trials (Table 2 presents recommendations).

Future directions for manipulation, masking and alterations of expectations

There are several ways to manipulate treatment expectation in psychedelic trials (a summary is provided in Table 3). One way is to use distinct verbal instructions in a balanced placebo design. The balanced placebo design, developed by Ross and colleagues in 1962 (ref. 97), is a study design used to investigate the psychological effects of a drug by manipulating participants' expectations of receiving the drug. In this design, participants are randomly assigned to one of four groups: (1) those who receive the actual drug and are told they are receiving it (true drug group); (2) those who receive a placebo and are told they are receiving the drug (placebo group); (3) those who receive the actual drug but are told they are receiving a placebo (hidden drug group); (4) those who receive a placebo and are told they are receiving a placebo (control group). By comparing the responses of these groups, researchers can determine how much the expectations of receiving a drug influence the reported outcome. This design helps control for the placebo and expectation effects and provides insights into both the

Table 3 | Future possible directions for manipulating, masking and altering expectations in psychedelic research

Approach	Description	Objective	Implementation	Challenges/risks
Balanced placebo design	Randomly assigns participants to four groups (true drug, placebo, hidden drug, control) to manipulate expectations	Isolate treatment efficacy by comparing the influence of expectations	Requires authorized deception, naive participants, use of microdoses	Requires authorized deception, participants must be naive
SPCD	Involves two stages: initial randomization to treatment or placebo, followed by re-randomization of placebo non-responders	Minimize expectations and placebo effects, enhance validity of study outcomes	Two-stage design with re-randomization of placebo non-responders, ensuring minimal expectation bias in Stage 2	Complex to design and implement, requires more resources, longer study duration, ethical concerns with re-randomization, and potential for higher dropout rates
Overt–covert design	Administer drug/placebo without participant knowledge of treatment timing	Separate active treatment from psychosocial effects	Provide distinct instructions on treatment onset to mask expectations	High risk of unblinding
Use of anesthesia	Anesthetize participants to achieve blinding, thus silencing expectations	Optimize blinding by preventing participant awareness	Suitable for trials involving surgical procedures	Logistical complexities, potential synergic effects of anesthetics
XR	Utilize VR to simulate psychedelic experiences without the pharmacological effects	Acclimate participants to sensory distortions associated with psychedelics	Create optimal VR environments for sessions, use as a non-pharmacological control	Risk of interactions with psychedelics with an amplification of cyber-sickness

pharmacological and psychological effects of a drug. In a hypothetical trial of a psychedelic-assisted therapy, this design would allow for the determination of the 'true' treatment effect by comparing the relative differences in objective and subjective outcomes between the groups. The balanced placebo design would allow researchers to isolate treatment efficacy under both reduced (treatment given as a placebo) and augmented (treatment given as treatment) expectation effects on symptom and experiential modifications. Implementing this design in real-world settings could require authorized deception in obtaining consent from prospective study participants, participants to be naive to the experiential effects of psychedelics to minimize unblinding, and the use of microdoses to optimize the separation of expectation versus drug effects in this 2 × 2 factorial design.

Alternately, one could leverage the sequential parallel comparison design (SPCD) to minimize expectations in Stage 2 of this design. The SPCD involves two stages. In Stage 1, participants are randomly assigned to receive either the treatment or placebo. Those who do not respond to the placebo in Stage 1 are re-randomized in Stage 2 to either continue with the placebo or switch to the treatment. This design helps to control for placebo responses and minimizes participant expectations by ensuring that non-responders to the placebo are given another chance to receive the active treatment. By using SPCD, researchers can better differentiate between the true effects of the treatment and the placebo responses, thus enhancing the validity of the study outcomes[98].

What about masking expectations by administering a psychedelic drug or placebo while the study participant is unaware of being treated?

The overt–covert treatment administration procedure separates active treatment from psychosocial effects without any placebo treatment[26,99,100]. In pain medicine, morphine delivered along with the information 'the treatment that you are about to receive is potent in relieving your pain' induced a higher pain-reduction effect than delivering the same dose of morphine while the patient was unaware of the onset of the delivery of morphine[26]. For the covert condition, the onset of the delivery of the treatment remains unknown, but participants know that they are being treated[101]. Giving distinct instruction on the onset of the delivery of the treatment may help masking the effect of expectations. However, the risk of unblinding is high.

Although it may sound a paradoxical practice, anesthetizing study participants could lead to the greatest degree of blinding. A recent study by Lii and colleagues compared the effects of ketamine with placebo on depression in subjects undergoing anesthesia related to a surgical procedure[102]. Although unconventional, the idea of using anesthesia as a control arm could 'silence' expectations. Lii and colleagues observed that over 50% of individuals with moderate to severe major depressive disorder experienced antidepressant improvement 24 h after receiving a single sub-anesthetic dose of ketamine[102]. However, an equal proportion of participants in the placebo group also demonstrated a response within a day of treatment. The use of anesthesia could enable the optimization of blinding, although this presents its own set of limitations and challenges. For outpatient trials in particular, implementing anesthesia becomes logistically complex, with logistical hurdles, and synergistic/antagonistic effects of the anesthetics cannot be excluded.

Finally, we could alter psychedelic-like experiences by adding an extended reality (XR) tool to the trial. XR is a digital device that affords users the sensation of being immersed in or transported into interactive, three-dimensional worlds in a variety of imaginary environments[103]. This technology is becoming popular in medicine[104]. XR—for example, virtual reality (VR)—could be an effective tool for acclimating participants who have never experienced hallucinogens to the sensory distortions associated with psychedelic states in clinical trials. Recognizing the crucial influence of the 'setting' on psychedelic treatment outcomes, VR can be leveraged to create optimal environments for psychedelic sessions[105]. VR, which is safe[106], could mimic the phenomenological aspects of psychedelic drugs without inducing the pharmacological effects[107] that underlie the drugs' therapeutic effects, thus allowing separation of the psychedelic experience from the pharmacological effects of the drug under investigation.

Conclusions

The investigation of diverse control arms in psychedelic trials necessitates a careful balance between maintaining blinding, ensuring safety and accurately assessing efficacy and outcomes. Addressing these methodological challenges is crucial for the advancement of psychedelic research and medicine. The integration of strategies such as dose–response curves, placebos and the measurement of expectations, along with innovative approaches such as XR, can enhance the reliability and generalizability of findings from clinical trials. By implementing rigorous trial designs and comprehensive control measures, we can better understand the therapeutic potential of psychedelics, ensuring their safe and effective use in clinical practice.

References

1. The promise and perils of psychedelics. *N. Engl. J. Med.* **388**, e24 (2023); https://doi.org/10.1056/NEJMp2300936

2. Mullard, A. MDMA scores PTSD success in a landmark phase III trial. *Nat. Rev. Drug Discov.* **20**, 414 (2021).
3. Mitchell, J. M. et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat. Med.* **27**, 1025–1033 (2021).
4. Barber, G., Nemeroff, C. B. & Siegel, S. A case of prolonged mania, psychosis and severe depression after psilocybin use: implications of increased psychedelic drug availability. *Am. J. Psychiatry* **179**, 892–896 (2022).
5. Goodwin, G. M. et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *N. Engl. J. Med.* **387**, 1637–1648 (2022).
6. Watson, C. The psychedelic remedy for chronic pain. *Nature* **609**, S100–S102 (2022).
7. Kurtz, J. S. et al. The use of psychedelics in the treatment of medical conditions: an analysis of currently registered psychedelics studies in the American Drug Trial Registry. *Cureus* **14**, e29167 (2022).
8. Olson, D. E. Psychoplastogens: a promising class of plasticity-promoting neurotherapeutics. *J. Exp. Neurosci.* **12**, 1179069518800508 (2018).
9. Aguilar, M. A., Garcia-Pardo, M. P. & Parrott, A. C. Of mice and men on MDMA: a translational comparison of the neuropsychobiological effects of 3,4-methylenedioxymethamphetamine ('Ecstasy'). *Brain Res.* **1727**, 146556 (2020).
10. Hess, E. M., Riggs, L. M., Michaelides, M. & Gould, T. D. Mechanisms of ketamine and its metabolites as antidepressants. *Biochem. Pharmacol.* **197**, 114892 (2022).
11. Levinstein, M. R. et al. Mu opioid receptor activation mediates (*S*)-ketamine reinforcement in rats: implications for abuse liability. *Biol. Psychiatry* **93**, 1118–1126 (2023).
12. Lumsden, E. W. et al. Antidepressant-relevant concentrations of the ketamine metabolite (2*R*,6*R*)-hydroxynorketamine do not block NMDA receptor function. *Proc. Natl Acad. Sci. USA* **116**, 5160–5169 (2019).
13. Zanos, P. & Gould, T. D. Intracellular signaling pathways involved in (*S*)- and (*R*)-ketamine antidepressant actions. *Biol. Psychiatry* **83**, 2–4 (2018).
14. Zanos, P. et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* **533**, 481–486 (2016).
15. Mitchell, J. M. et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Focus* **21**, 315–328 (2023).
16. Mitchell, J. M. et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nat. Med.* **29**, 2473–2480 (2023).
17. Reardon, S. Psychedelic drug MDMA moves closer to US approval following success in PTSD trial. *Nature* https://doi.org/10.1038/d41586-023-02886-x (2023).
18. Slomski, A. MDMA-assisted therapy highly effective for PTSD. *J. Am. Med. Assoc.* **326**, 299 (2021).
19. Reardon, S. MDMA therapy for PTSD rejected by FDA panel. *Nature* https://doi.org/10.1038/d41586-024-01622-3 (2024).
20. Kupferschmidt, K. Psychedelics field looks ahead after FDA advisers' rejection. *Science* **384**, 1158–1159 (2024).
21. Mullard, A. MDMA-assisted therapy for PTSD passes phase III trial. *Nat. Rev. Drug Discov.* **22**, 863 (2023).
22. Madero, S. & Alvarez, O. D. Premise, promise and challenges of MDMA assisted therapy for PTSD. *Eur. Neuropsychopharmacol.* **70**, 19–20 (2023).
23. Colloca, L. & Barsky, A. J. Placebo and nocebo effects. *N. Engl. J. Med.* **382**, 554–561 (2020).
24. Amanzio, M. & Benedetti, F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J. Neurosci.* **19**, 484–494 (1999).
25. Eippert, F. et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron* **63**, 533–543 (2009).
26. Colloca, L., Lopiano, L., Lanotte, M. & Benedetti, F. Overt versus covert treatment for pain, anxiety and Parkinson's disease. *Lancet Neurol.* **3**, 679–684 (2004).
27. Benedetti, F., Amanzio, M., Casadio, C., Oliaro, A. & Maggi, G. Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. *Pain* **71**, 135–140 (1997).
28. Benedetti, F., Amanzio, M., Vighetti, S. & Asteggiano, G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J. Neurosci.* **26**, 12014–12022 (2006).
29. Olson, J. A., Suissa-Rocheleau, L., Lifshitz, M., Raz, A. & Veissiere, S. P. L. Tripping on nothing: placebo psychedelics and contextual factors. *Psychopharmacology (Berl.)* **237**, 1371–1382 (2020).
30. Studerus, E., Kometer, M., Hasler, F. & Vollenweider, F. X. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. *J. Psychopharmacol.* **25**, 1434–1452 (2011).
31. Neogi, T. & Colloca, L. Placebo effects in osteoarthritis: implications for treatment and drug development. *Nat. Rev. Rheumatol.* **19**, 613–626 (2023).
32. Colloca, L. Tell me the truth and I will not be harmed: informed consents and nocebo effects. *Am. J. Bioeth.* **17**, 46–48 (2017).
33. Colloca, L. Nocebo effects can make you feel pain. *Science* **358**, 44 (2017).
34. Colloca, L. The nocebo effect. *Annu. Rev. Pharmacol. Toxicol.* **64**, 171–190 (2024).
35. Vase, L., Amanzio, M. & Price, D. D. Nocebo vs. placebo: the challenges of trial design in analgesia research. *Clin. Pharmacol. Ther.* **97**, 143–150 (2015).
36. Vase, L. et al. Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: a meta-analysis of the individual data from nine industrially sponsored trials. *Pain* https://doi.org/10.1097/j.pain.0000000000000217 (2015).
37. Colloca, L. Placebo, nocebo and learning mechanisms. *Handb. Exp. Pharmacol.* **225**, 17–35 (2014).
38. Colloca, L. & Miller, F. G. Role of expectations in health. *Curr. Opin. Psychiatry* **24**, 149–155 (2011).
39. Dolgin, E. Fluctuating baseline pain implicated in failure of clinical trials. *Nat. Med.* **16**, 1053 (2010).
40. Huneke, N. T. M., van der Wee, N., Garner, M. & Baldwin, D. S. Why we need more research into the placebo response in psychiatry. *Psychol. Med.* **50**, 2317–2323 (2020).
41. Rosenzweig, P., Brohier, S. & Zipfel, A. The placebo effect in healthy volunteers: influence of experimental conditions on the adverse events profile during phase I studies. *Clin. Pharmacol. Ther.* **54**, 578–583 (1993).
42. Hauser, W., Sarzi-Puttini, P., Tolle, T. R. & Wolfe, F. Placebo and nocebo responses in randomised controlled trials of drugs applying for approval for fibromyalgia syndrome treatment: systematic review and meta-analysis. *Clin. Exp. Rheumatol.* **30**, 78–87 (2012).
43. Rief, W., Avorn, J. & Barsky, A. J. Medication-attributed adverse effects in placebo groups: implications for assessment of adverse effects. *Arch. Intern. Med.* **166**, 155–160 (2006).
44. Fava, M., Evins, A. E., Dorer, D. J. & Schoenfeld, D. A. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies and a novel study design approach. *Psychother. Psychosom.* **72**, 115–127 (2003).
45. Colloca, L. The placebo effect in pain therapies. *Annu. Rev. Pharmacol. Toxicol.* **59**, 191–211 (2019).
46. Bingel, U. et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci. Transl. Med.* **3**, 70ra14 (2011).

47. Petersen, G. L. et al. Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. *Pain* **155**, 2687–2698 (2014).
48. Linde, K. et al. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain* **128**, 264–271 (2007).
49. Wartolowska, K. et al. Use of placebo controls in the evaluation of surgery: systematic review. *Br. Med. J.* **348**, g3253 (2014).
50. Cormier, S., Lavigne, G. L., Choinière, M. & Rainville, P. Expectations predict chronic pain treatment outcomes. *Pain* **157**, 329–338 (2016).
51. Metaxa, A. M. & Clarke, M. Efficacy of psilocybin for treating symptoms of depression: systematic review and meta-analysis. *Br. Med. J.* **385**, e078084 (2024).
52. Young, N. S., Ioannidis, J. P. & Al-Ubaydli, O. Why current publication practices may distort science. *PLoS Med.* **5**, e201 (2008).
53. Fanelli, D., Costas, R. & Ioannidis, J. P. Meta-assessment of bias in science. *Proc. Natl Acad. Sci. USA* **114**, 3714–3719 (2017).
54. Schooler, J. Unpublished results hide the decline effect. *Nature* **470**, 437–437 (2011).
55. Harrison, R. K. Phase II and phase III failures: 2013–2015. *Nat. Rev. Drug Discov.* **15**, 817–818 (2016).
56. Scott, A. J., Sharpe, L., Quinn, V. & Colagiuri, B. Association of single-blind placebo run-in periods with the placebo response in randomized clinical trials of antidepressants: a systematic review and meta-analysis. *JAMA Psychiatry* **79**, 42–49 (2022).
57. Iovieno, N. & Papakostas, G. I. Correlation between different levels of placebo response rate and clinical trial outcome in major depressive disorder: a meta-analysis. *J. Clin. Psychiatry* **73**, 1300–1306 (2012).
58. Griffiths, R. R., Richards, W. A., McCann, U. & Jesse, R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl.)* **187**, 268–283 (2006).
59. Papakostas, G. I. et al. Efficacy of esketamine augmentation in major depressive disorder: a meta-analysis. *J. Clin. Psychiatry* **81**, 19r12889 (2020).
60. Bauer, M., El-Khalili, N., Datto, C., Szamosi, J. & Eriksson, H. A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. *J. Affect. Disord.* **127**, 19–30 (2010).
61. Soliman, P. S., Curley, D. E., Capone, C., Eaton, E. & Haass-Koffler, C. L. In the new era of psychedelic assisted therapy: a systematic review of study methodology in randomized controlled trials. *Psychopharmacology (Berl.)* **241**, 1101–1110 (2024).
62. Grob, C. S. et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch. Gen. Psychiatry* **68**, 71–78 (2011).
63. Ross, S. et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J. Psychopharmacol.* **30**, 1165–1180 (2016).
64. Holze, F., Gasser, P., Muller, F., Dolder, P. C. & Liechti, M. E. Lysergic acid diethylamide-assisted therapy in patients with anxiety with and without a life-threatening illness: a randomized, double-blind, placebo-controlled phase II study. *Biol. Psychiatry* **93**, 215–223 (2023).
65. Fava, M. et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Mol. Psychiatry* **25**, 1592–1603 (2020).
66. Bogenschutz, M. P. et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry* **79**, 953–962 (2022).
67. Jensen, J. S., Bielefeldt, A. O. & Hrobjartsson, A. Active placebo control groups of pharmacological interventions were rarely used but merited serious consideration: a methodological overview. *J. Clin. Epidemiol.* **87**, 35–46 (2017).
68. Laursen, D. R. et al. Impact of active placebo controls on estimated drug effects in randomised trials: a systematic review of trials with both active placebo and standard placebo. *Cochrane Database Syst. Rev.* **3**, MR000055 (2023).
69. Lembo, A. et al. Open-label placebo vs double-blind placebo for irritable bowel syndrome: a randomized clinical trial. *Pain* **162**, 2428–2435 (2021).
70. Carvalho, C. et al. Open-label placebo for chronic low back pain: a 5-year follow-up. *Pain* **162**, 1521–1527 (2021).
71. Disley, N., Kola-Palmer, S. & Retzler, C. A comparison of open-label and deceptive placebo analgesia in a healthy sample. *J. Psychosom. Res.* **140**, 110298 (2021).
72. Specker Sullivan, L. More than consent for ethical open-label placebo research. *J. Med. Ethics* https://doi.org/10.1136/medethics-2019-105893 (2020).
73. Kaptchuk, T. J. Open-label placebo: reflections on a research agenda. *Perspect. Biol. Med.* **61**, 311–334 (2018).
74. Kaptchuk, T. J. & Miller, F. G. Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits?. *Br. Med. J.* **363**, k3889 (2018).
75. Flowers, K. M. et al. Conditioned open-label placebo for opioid reduction after spine surgery: a randomized controlled trial. *Pain* **162**, 1828–1839 (2021).
76. Shiffman, S., Stone, A. A. & Hufford, M. R. Ecological momentary assessment. *Annu. Rev. Clin. Psychol.* **4**, 1–32 (2008).
77. Sarpatwari, A., Kohli, S., Tu, S. S. & Kesselheim, A. S. Patents on risk evaluation and mitigation strategies for prescription drugs and generic competition. *J. Am. Med. Assoc.* **331**, 976–978 (2024).
78. Geers, A. L., Spotts, E. K., Vang, M., Mayer, S. R. & Miller, F. G. The use of authorized concealment to minimize nocebo side effects: a survey of US public attitudes. *Psychother. Psychosom.* **92**, 391–398 (2023).
79. Blease, C. Authorized concealment and authorized deception: well-intended secrets are likely to induce nocebo effects. *Am. J. Bioeth.* **15**, 23–25 (2015).
80. Bedford, T. et al. Attitudes toward a pre-authorized concealed opioid taper: a qualitative analysis of patient and clinician perspectives. *Front. Psychiatry* **13**, 820357 (2022).
81. Goo, S. J. et al. Attitudes and perceptions toward authorized deception: a pilot comparison of healthy controls and fibromyalgia patients. *Pain Med.* **21**, 794–802 (2020).
82. Papakostas, G. I. & Fava, M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *Eur. Neuropsychopharmacol.* **19**, 34–40 (2009).
83. Palhano-Fontes, F. et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychol. Med.* **49**, 655–663 (2019).
84. Bottemanne, H. et al. Evaluation of early ketamine effects on belief-updating biases in patients with treatment-resistant depression. *JAMA Psychiatry* **79**, 1124–1132 (2022).
85. Carhart-Harris, R. et al. Trial of psilocybin versus escitalopram for depression. *N. Engl. J. Med.* **384**, 1402–1411 (2021).
86. Szigeti, B. et al. Assessing expectancy and suggestibility in a trial of escitalopram v. psilocybin for depression. *Psychol. Med.* **54**, 1717–1724 (2024).
87. Colloca, L., Nikayin, S. & Sanacora, G. The intricate interaction between expectations and therapeutic outcomes of psychedelic agents. *JAMA Psychiatry* **80**, 867–868 (2023).

88. Yu, L. et al. Development of short forms from the PROMIS™ sleep disturbance and sleep-related impairment item banks. *Behav. Sleep Med.* **10**, 6–24 (2012).
89. Alberts, J. et al. Development of the generic, multidimensional Treatment Expectation Questionnaire (TEX-Q) through systematic literature review, expert surveys and qualitative interviews. *BMJ Open* **10**, e036169 (2020).
90. Shedden-Mora, M. C. et al. The treatment expectation questionnaire (TEX-Q): validation of a generic multidimensional scale measuring patients' treatment expectations. *PLoS ONE* **18**, e0280472 (2023).
91. Colloca, L. et al. Prior therapeutic experiences, not expectation ratings, predict placebo effects: an experimental study in chronic pain and healthy participants. *Psychother. Psychosom.* **89**, 371–378 (2020).
92. Atlas, L. Y. & Wager, T. D. How expectations shape pain. *Neurosci. Lett.* **520**, 140–148 (2012).
93. Fields, H. L. How expectations influence pain. *Pain* **159**, S3–S10 (2018).
94. Colloca, L. & Miller, F. G. Harnessing the placebo effect: the need for translational research. *Philos. Trans. R. Soc. B Biol. Sci.* **366**, 1922–1930 (2011).
95. Crum, A. & Zuckerman, B. Changing mindsets to enhance treatment effectiveness. *J. Am. Med. Assoc.* **317**, 2063–2064 (2017).
96. Kaptchuk, T. J. & Miller, F. G. Placebo effects in medicine. *N. Engl. J. Med.* **373**, 8–9 (2015).
97. Ross, S., Krugman, A. D., Lyerly, S. B. & Clyde, D. J. Drugs and placebos: a model design. *Psychol. Rep.* **10**, 383–392 (1962).
98. Fava, M. How should we design future mechanistic and/or efficacy clinical trials? *Neuropsychopharmacology* **49**, 197–204 (2024).
99. Benedetti, F. et al. Open versus hidden medical treatments: the patientas knowledge about a therapy affects the therapy outcome. *Prev. Treat.* **6**, 1a (2003).
100. Benedetti, F. et al. Autonomic and emotional responses to open and hidden stimulations of the human subthalamic region. *Brain Res. Bull.* **63**, 203–211 (2004).
101. Colloca, L. et al. Veteran engagement in opioid tapering research: a mission to optimize pain management. *Pain Rep.* **6**, e932 (2021).
102. Lii, T. R. et al. Randomized trial of ketamine masked by surgical anesthesia in patients with depression. *Nat. Ment. Health* **1**, 876–886 (2023).
103. Honzel, E. et al. Virtual reality, music and pain: developing the premise for an interdisciplinary approach to pain management. *Pain* **160**, 1909–1919 (2019).
104. Persky, S. & Colloca, L. Medical extended reality trials: building robust comparators, controls and sham. *J. Med. Internet Res.* **25**, e45821 (2023).
105. Aday, J. S., Davoli, C. C. & Bloesch, E. K. Psychedelics and virtual reality: parallels and applications. *Ther. Adv. Psychopharmacol.* **10**, 2045125320948356 (2020).
106. Gomez-Busto, F. J. & Ortiz, M. I. Virtual reality and psychedelics for the treatment of psychiatric disease: a systematic literature review. *Clin. Neuropsychiatry* **17**, 365–380 (2020).
107. Kwan, A. C., Olson, D. E., Preller, K. H. & Roth, B. L. The neural basis of psychedelic action. *Nat. Neurosci.* **25**, 1407–1419 (2022).

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L.C. and M.F. drafted the first synopsis. L.C. prepared the first draft. L.C. and M.F. finalized the manuscript. L.C. and M.F. confirm sole responsibility for the content.

Competing interests

L.C. declares no competing interests. M.F.'s disclosures are available at https://mghcme.org/maurizio-fava-bio-disclosure/.

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