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- Psychedelic Drugs as a Multidisciplinary Controversy
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Viewpoint Article

Psychedelic Drugs as a Multidisciplinary Controversy

Sydney McMullin

Psychedelic Drugs as a Multidisciplinary Controversy

Controversy surrounding psychedelic drugs is an interdisciplinary issue that spans across legal, medical, anthropological, and religious fields. Classical psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and mescaline were heavily researched and used as psychiatric treatments. While there were many flaws in the research methodologies and practices at the time, clinical trial data supports theories of clinical efficacy demonstrated by these drugs until they were classified as schedule I substances under the Comprehensive Drug Abuse Prevention and Control Act of 1970 by the FDA [1,2]. The halt in psychiatric research on psychedelic drugs became collateral damage to legislative backlash against growing rates of illicit consumption. +/-3,4-methylenedioxymethamphetamine (MDMA), another drug producing similar side effects to psilocybin and LSD, was banned shortly after. Human psychedelic research was put on pause until the early 1990s, but has since seen massive advancements.

Cultural Impact

Public opinion has seen similar trends as well. Psychedelics reached peak popularity during the mid-twentieth century, with more people than ever experimenting with their effects. They became a hallmark symbol of the counterculture movement that fostered a blend of eastern spirituality, Indigenous rituals, and particularly the use of psychedelics. As the "hippie movement" spread, especially in opposition to the unfolding of the Vietnam War, the use and infamy of psychedelics followed suit [3]. Even after legislative action was taken, outlawing their use, they continued to be a symbol of this anti-culture, anti-capitalist movement. The messages being transmitted portrayed the use of psychedelics as deviant behaviors associated with high crime rates, violence, and poor quality of living [4]. Public opinion at the time, and even in modern times, was heavily influenced by the agendas of mass media outlets and served as the primary source of education concerning the issue.

It has not been until recently that the dialogue surrounding psychedelics has shifted, and conversations surrounding their use have become more common to talk about publicly. In an article "Holiday Gift Guide 2021: Gifts for the Psychedelic Explorer", Siebert claimed that 2020 was the year psychedelics transitioned from covert, underground use to becoming mainstream [5]. As evident by an entire holiday gift guide devoted to psychedelic paraphernalia, it seems as though the pendulum of public opinion has swung. Financial analysts are even recommending switching investments to "shroom stocks," as they are surpassing the medical marijuana industry in terms of profitability [6].

Neurological and Behavioral Effects

These substances are primarily serotonergic agonists acting in the limbic and cortical regions of the brain. They affect the serotonin (5-HT2A) pathways in the pre-frontal cortex (PFC), which is responsible for high-level cognitive processing and self-monitoring behaviors [7]. They are also responsible for changes in perception, self-awareness, beliefs, visual and auditory disturbances, and related to mystical/profound experiences [8]. There is also significantly reduced activity in default-mode network structures, as shown by human neuroimaging studies [9]. However, much is still unknown about the mechanism of behavioral changes that occur as a result of psychedelic drugs.

While these psychedelic drugs are highly regulated due to their supposed high potential for abuse and adverse side effects, common media outlets and peer-reviewed studies alike have both present evidence supporting the incorporation of psychedelics into medicine and daily life because they do not have the same potential for abuse as other schedule I drugs, have historically functioned as a means of enlightenment and spiritual healing, and have shown success in therapeutic settings with treatment-resistant conditions.

Different Addiction Profile and Side Effects

It is well known that psychedelic and hallucinogenic drugs lack the same addiction profile that other recreational drugs possess, specifically other Schedule I drugs, giving them a lower potential for abuse. Historically speaking, the definition of abuse potential has shifted as theories of addiction have developed. Potential for abuse was historically defined by the presence of physical dependence and withdrawal, but has since shifted to looking at the behavioral effects of substance use and repeated self-administration [10]. This paradigmatic shift, brought about by new information and research, questions the stringent regulation placed on these substances. Based on a review of medical psilocybin, Johnson and colleagues recommended reducing psilocybin to a schedule IV classification, thus lowering the barriers to obtaining adequate treatment.

Psychedelic drugs are also not considered addictive substances because they operate on serotonergic receptors. Andersen et al. found that psychedelics like psilocybin show high levels of activity at 5-HT2a, 5-HT2c, and 5-HT1a/b receptors [11]. Psilocybin also has a low affinity for dopamine D2 receptors [10]. LSD shows activity at dopaminergic receptors, as well as 5-HT6 and 5-HT7 receptors. With the strong influence of serotonergically controlled behaviors, rather than dopamine in the brain, the reinforcing effects that contribute to addictive behaviors are negligible. Additionally, the effect of psilocybin and LSD on serotonin has also been tested by administering a 5-HT2a antagonist, ketanserin, which inhibits the mood-boosting effects of psilocybin and LSD [12]. This proves that by inhibiting serotonin activity in the brain, psilocybin and LSD activity are also inhibited.

Acting as a defense mechanism to intense, repeated serotonin activation, 5-HT2a receptors are downregulated and desensitized. Additionally the receptors decrease their affinity for 5-HT2a in the synapse, leading to decreased binding. Buchborn et al. found that this process, known as tachyphylaxis, produces near tolerance within 2-3 days of administration at high doses [13]. Unlike classically addictive substances, which generate dopaminergic sensitization that reinforces and escalates compulsive use, psychedelic-induced 5-HT2a downregulation diminishes the effect of subsequent doses. This creates the characteristic self-limiting pharmacological profile.

Another factor when considering potential for abuse is the level of dependence and withdrawal. While dependence is not formed, tolerance is developed rapidly to psilocybin and LSD. There is also little evidence of withdrawal [10, 14]. Since there is no dependence and intense craving sensations associated with consumption, the risk for addiction is minimal. In therapeutic programs where it would be used, it does not include prolonged daily administration as part of the treatment plan, so there would be little to no concern about developing tolerance.

Cognitive processes also help explain the lower potential for abuse of psychedelics. First, it is important to recognize that there is unpredictability in the individual's reaction to the drug. When it comes to the subjective experience of taking psychedelics, someone's reaction may not be consistent [15]. This

variability makes it hard for researchers to control, with cognitive and emotional state having such a significant impact on reaction [16]. When talking with a renowned psychedelic researcher at John Hopkins, Allen wrote that two people taking the same dose in the same setting can have two opposite reactions.

Although in behaviorist models of operant conditioning, the inconsistent and variable reinforcement promotes higher response rates, this kind of unpredictability is not what drives an addict's behavior. Regular heroin or methamphetamine users, they are motivated by the potent recall of a euphoric experience. This memory of previous experiences drives repeated administration, chasing the same experience [17]. Without this memory and reinforcement affecting behavior, addiction is not likely to form.

With respect to harm to self and others, psilocybin and LSD present the lowest rates of harm to self and others. When looking at physical, cognitive, and social harm to self, psilocybin ranked last, with other Schedule I drugs like methamphetamine and crack cocaine presenting the most harm to self [18, 19]. However, as with any medication or substance in the body, mild side effects have been reported, including headache, nausea, and vomiting. Since it is a serotonin agonist, there is a risk of serotonin syndrome and potential interactions with other psychoactive substances [20]. The more severe risks, such as prolonged hallucinations and psychosis, can be eliminated by using them in a safe and controlled environment, such as in a therapeutic setting.

Cultural shifts with the onset of the counterculture movement in the 1960s and 1970s played a large role in limiting research and public opinion for the next two decades. With the Controlled Substances Act of 1970, attitudes toward psychedelics shifted toward more negative beliefs, although they continued to be used in underground settings. The information surrounding side effects, both positive and negative, comes largely from word of mouth. There are forums on the internet with boards offering advice for things like affirmations to recite before a psilocybin-induced trip. Most of the profoundly negative stories surrounding bad trips have become urban legends spread through the grapevine and community of users. Similarly, stories of the mind-expanding experiences motivate people to experiment with psychedelics. A major disclaimer that is not emphasized enough in the media and personal experiences is the variability of reactions people can have, which the lack of understanding and education surrounding the drugs can contribute to the dangerous and harmful side effects associated with psychedelics. There should be more media representation concerning safety for recreational use, given its rise in consumption, especially among young adults.

Historical means of enlightenment and spiritual healing

Psychedelics have been used for spiritual purposes for centuries and continue to be used for such purposes today. They act as a gateway to transcendent experiences that expand one's sense of self and connect to spiritual forces in their environment [21]. In the last 10 years, there has been a shift from focusing on spirituality less in the context of organized religion to focusing on the individual spiritual journey and healing. Additionally, there is a greater priority placed on the self and searching for inner-human capacity, known to some as "the cult of the self" [22]. These have grown in popularity as holistic wellness has received more attention in the media.

Spiritual healing involves restoring an organism's energy and dates to Vedic times through practices such as unblocking chakras in the body. According to this theory, chakras are energy fields in the body that, when

"blocked," can cause somatic and psychological conditions. There are additional theories that relate different chakras in the body to endocrine glands, although none of these have been empirically proven [23]. Chakras can be healed through mindfulness meditation, yoga, and psychedelic use.

One of the hallmark traits of a psychedelic trip is the mystical experience and spiritual growth that come as a result. Participants in psychedelic research studies consistently rank these experiences as one of the top spiritual experiences and one of the most profound experiences of their lives [24]. Participants report increases in mood, deeper appreciation for the world around them, and improved relationships with themselves and others [25-29].

In addition to spiritual growth, there are societal benefits . Those who consistently use psychedelics, known as Psychonauts, possess spiritually influenced beliefs and attitudes about life that are strengthened as a result of their psychedelic trips. Ironically, it seems as though this functions, in some cases, as a protective measure against additional drug-seeking behaviors [30]. In addition to reduced drug-related problems, studies have shown that psychedelics are the drug least responsible for criminal activity in general [18, 31].

Many celebrities have become more open concerning their experiences with psychedelics, whether as a means of spiritual growth and healing or for recreational use. While the individual experiences vary, most report having enlightening and positive experiences. For example, country artist Kasey Musgraves reported that LSD has helped her find more meaning and a deeper appreciation for life [32]. Another actor and songwriter, Reggie Watts, shared that it opened his mind to a deeper understanding of the universe, and the changes he implemented as a result [33]. On the *Joe Rogan Experience* podcast, Miley Cyrus said that she experienced a major panic attack after taking psilocybin and marijuana [34]. The conversation surrounding psychedelic use is becoming candid in a way that allows people to become educated about the drug, and, should they choose to use it either for recreation or spiritual growth, they can have an optimal experience.

Therapeutic Intervention for Treatment-Resistant Conditions

Psychedelic research began studying the neurological correlates of schizophrenia and the basis of psychosis. This broadened to seeing how it impacted disorders like major depressive disorder (MDD), bipolar disorder, PTSD, obsessive-compulsive disorder (OCD), anxiety, and substance use disorders like alcoholism. While methodological practices for studies completed in the 1950s and 60s would not meet validity standards today, there was overwhelming data that supported psychedelic-assisted therapy. However, due to the equally overwhelming recreational use, it was banned, and research was effectively halted.

Not until recently, with updated research practices and technology, has research gained traction in medicine, but in the legal world as well. The state of Texas has begun investing funds and resources in MDMA treatment for veterans with PTSD [35]. Additionally, financial trend analysts predict that the psychedelic industry will surpass the medical marijuana market by monetizing both the production of the drugs and their therapeutic administration [6]. While ethically questionable, the psychedelic industry is indeed expanding in ways medical marijuana could not.

Psychedelics Altering Self and Social Processing

Psychedelics also allow for a softening and alteration of staunchly held beliefs. Metaphysical beliefs surrounding health, religion, philosophy, and education are explored

through experiences with psychedelic drugs. Some of these metaphysical beliefs can be harmful and maladaptive, and trigger psychiatric conditions such as depression and PTSD. Things like psychedelic-assisted therapy put patients in an impressionable state where they can explicitly discover these implicit beliefs [26]. It is this suggestibility that allows for confidence in these beliefs to be relaxed and for those beliefs to be changed. Not only can beliefs be changed, but behavioral changes can come as a result of psychedelic assisted therapy [36].

Another key alteration to self-processing is the dissolution of the ego. This produces a "decentering" effect that allows users to internalize a broader spectrum of beliefs and emotions. According to Vollenweider & Preller, this is thought to be especially helpful for someone with depression or PTSD who experiences intrusive thoughts and rumination [36]. These cognitive changes can translate to reduced levels of rejection sensitivity and empathy towards others [37]. It is these changes in self-processing that may cause changes in social cognition, both of which contribute to therapeutic success.

Psychedelics Altering Emotional Processing

Psychedelic drugs cause a cascade of physiological changes in emotional processing. Kraehenmann et al. found that with psilocybin, there is a reduction in processing of negative stimuli in the amygdala and alterations in connectivity between structures in the limbic system [38]. This was shown by reduced response rates to faces with a frown or angry look. However, Bershad et al. reported a positive correlation between increased connectivity strength in the amygdala and middle frontal gyrus and positive mood with LSD [39]. Both studies suggest that emotional alterations occur within limbic circuits, although the exact mechanism remains unclear. From a phenomenological standpoint, maladaptive beliefs can be deconstructed and changed by looking at them from an outside point of view, as users commonly report out-of-body-like experiences. However, additional studies are needed to investigate further the changes in emotional processing in other, more extreme, psychiatric disorders.

There is also evidence of neuroplasticity in the brain due to psychedelic use. This occurs because of enhanced AMPA activation, due to NMDA receptor blockages causing glutamate release by drugs like ketamine. Through the increase in presynaptic glutamate levels in the prefrontal-limbic circuits, it is possible that this is the location where the neuroplastic changes occur that are responsible for the therapeutic mechanism of drugs like psilocybin and ketamine [40]. By causing changes at the synaptic level, this supports the biological hypothesis underlying mood disorders.

Psychedelic-Assisted Psychotherapy

When used in conjunction with psychotherapy, patients seem to experience marked decreases in psychiatric symptoms with psychedelic use. Positive therapeutic outcomes have been demonstrated in studies treating alcoholism and cigarette smoking, PTSD, OCD, and anxiety [11, 29, 35, 41-44]. Evidence shows that psychedelic-assisted psychotherapy is better at treating MDD than traditional pharmacological approaches and psychotherapy, and even when compared to medicine and psychotherapy combined [45, 46]. However, it is hard to control the individual experiences that people will have, which presents a limitation in generalizing conclusions about psychedelic research because it may vary on a case-by-case basis.

There are limitations to these studies, such as smaller sample sizes and the placebo effect of the drug itself. The mechanism of the behavioral effects of psychedelics

remains largely unknown. In conditions like alcoholism, the addiction to one substance is being overridden by the influences of another. It brings into question whether it is the drug itself causing changes to the behavior, or if the previously held beliefs and knowledge of the drug accounts for the positive experience and change. Participants in the studies typically were more open to trying experimental psychedelic therapy, so embracing the experience could play a larger role in predicting the outcome than is given credit. Conversely, someone who is staunchly against psychedelic experimentation could have a different experience because of their more rigid mindset.

Both common media outlets and peer-reviewed sources emphasized the importance of using psychedelics in a controlled environment, and if using in a therapeutic setting, under the guidance of someone who is trained to work with patients in altered states of consciousness [20]. If using recreationally or for ritual purposes, being in a safe physical environment will minimize the risk of any potential danger to yourself or others.

Conclusion

With these drugs seeming to be a miracle "cure-all" for psychiatric conditions, there is a reason why experiments with them are extremely selective in the criteria for inclusion. They are still psychoactive substances that alter an individual's state of consciousness. These results should be analyzed with caution, as limitations were present in each study, such as small sample sizes, limited to a narrow demographic or condition, and limited interaction with other medications. For practical implementation, responsibilities such as work and family, and the effects they have on other medications, need to be taken into consideration.

This also raises the question whether the well-intentioned, systematic regulations that would allow for safe use in medicine would be consistently implemented at the individual level. Opioids were introduced to target severe pain, and they succeeded. So much so that despite stringent regulations and laws placed on their distribution, there remains an opioid epidemic in America. While psychedelics do not present the same potential for abuse and have been used for centuries in religious contexts without those same repercussions, there is the same risk of inconsistency and lax rule-following at an individual level between the clinician and patient. The potential for adverse effects is increased, and the optimal benefit of these controversial substances is minimized when they are not used in a controlled setting, under proper guidance.

AUTHOR INFORMATION

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Editorial

Equal or Unequal? Concerns About the Meta-Analysis of Psychedelic-Assisted Therapy Compared to Open-Label Antidepressants

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On March 18th, 2026, JAMA Psychiatry published a systematic review and meta-analysis entitled "Psychedelic Therapy vs Antidepressants for the Treatment of Depression Under Equal Unblinding Conditions [1]." The piece arrives in the thick of the ongoing psychedelic renaissance, only months removed from the FDA's 2024 rejection of MDMA-assisted psychotherapy for posttraumatic stress disorder, while phase-3 controversies still simmer [2] and while popular media continues to amplify enthusiastic claims about psilocybin, ayahuasca, and kindred compounds as potential game-changers for major depressive disorder (MDD). At first glance, the authors' central move, stacking within-arm symptom change from psychedelic-assisted therapy (PAT) trials (which are essentially always open-label because of unmistakable subjective effects) against open-label traditional antidepressant (TAD) trials, looks like a smart way to tackle the well-known functional-unblinding problem in PAT research. However, a careful reading reveals important limitations that weaken both the reach and the force of the conclusions. These limitations involve clear differences in how treatments are delivered, the patients studied, the time frames examined, and the outcomes measured; an over-reading of statistical similarity as true clinical sameness; and too little attention to PAT's distinctive strengths in speed, lasting benefit, and patient-focused results.

This editorial does not reject the paper's value. Functional unblinding matters, as Szigeti has shown in earlier studies on expectancy and MDMA guessing bias [3]. The analysis rightly points out that the apparent PAT-versus-placebo gap in standard blinded trials looks larger than the corresponding gap in TAD trials. Even so, the study's design and framing risk giving readers an incomplete view of the matter, one that could unintentionally slow the progress of valuable research efforts or sway regulatory and clinical decisions without providing the full measure of nuance the topic demands.

PAT involves a high dose of a classic psychedelic (psilocybin, LSD, DMT/ayahuasca) or an empathogen (MDMA) together with structured psychotherapy—usually 6–10 or more hours of preparation, a supervised dosing session with two therapists, and follow-up integration work. Clinical trials of psychedelic compounds routinely report substantial reductions on the Hamilton Depression Rating Scale (HAM-D-17), often a decrease of 10 to 15 points on average [4]. This decrease far exceeds the typical decrease seen between active antidepressants and placebo in TAD studies. Critics have pointed out that functional unblinding is nearly impossible to prevent in these settings, with more than 90% of participants correctly identifying the active psychedelic compound due to the unmistakable subjective effects of the compounds. This functional unblinding amplifies improvement by increasing the expectations of patients who enrolled in the studies in the hopes of receiving benefits from the psychedelic compound [5].

The authors' approach was to level the playing field by comparing PAT with open-label TAD trials (where everyone knows they are receiving active medication). The authors conducted a PubMed search in March 2024 and used the framework described by Cipriani et al. [6]. They restricted inclusion to outpatient adults aged 18-65 years diagnosed with major depressive disorder. They excluded participants with comorbid conditions except for anxiety. These exclusionary diagnoses included a history of psychosis or inpatient treatment and limited the use of run-in periods or combination therapies. After dual extraction, Bayesian and frequentist mixed-effects modeling, and conversion to HAM-D-17 scores, the main result was straightforward: PAT (8 trials, 249 patients) showed no meaningful advantage over open-label TADs (16 trials, 7,921 patients), but rather a small, insignificant 0.3-point difference favoring TADs (95 % CI −1.39 to 1.98; P = .73). Open-label TADs beat blinded TADs by 1.3 points (P = .04; 144 trials, 31,792 patients), but PAT displayed no such open-versus-blinded difference. Both groups achieved "robust, clinically meaningful" gains. The abstract, therefore, concludes that the data "argue against highly optimistic narratives surrounding PAT and highlight the importance of blinding integrity."

The reasoning is straightforward and was pre-registered from the outset. The results also align with the single direct head-to-head trial of a psychedelic vs. a selective serotonin reuptake inhibitor (SSRI) published in 2021 [7]. That study found no significant difference in the primary QIDS outcome between psilocybin and escitalopram, even though several secondary measures favored psilocybin [7]. Though

concerns about the use of the QIDS as the primary outcome measure have been extensively detailed, this trial's result may primarily be driven by choosing the wrong outcome measurement tool, as opposed to the ineffectiveness of the psychedelic compound [8].

The authors reported only minor deviations in the supplemental methods. They fully adhered to PRISMA guidelines, conducted independent dual screening and data extraction, used a conservative scale-conversion approach with an SD correlation of 0.5, and applied both Bayesian and frequentist mixed-effects modeling. In addition, the strict inclusion criteria helped reduce heterogeneity that would otherwise have been expected. The much larger pool of traditional antidepressant (TAD) trials provided the statistical power that the smaller psychedelic-assisted therapy (PAT) literature, with only eight qualifying trials, could not achieve alone. Sensitivity analyses that removed treatment-resistant depression subsets or restricted the data to HAM-D scores reportedly preserved the null finding of no difference between TAD and PAT. The authors openly noted the shorter PAT follow-up window (mean 3.4 weeks versus 8.1 weeks for TADs) and the modest baseline severity gap (HAM-D 21.3 versus 22.7), then adjusted for the latter. They also correctly traced much of the inflated PAT–placebo separation to expectancy effects, estimating that roughly 55% of the apparent advantage in blinded trials stems from "placebo suppression" in the control arm [1].

Psychedelics vs. Psychedelic-Assisted Psychotherapy

PAT is not simply drug treatment. It is a full multimodal package. The medicine opens altered states, but the extensive protocolized psychotherapy supplies the structure. Standard protocols from centers such as COMPASS Pathways, Johns Hopkins, and Imperial College typically include one or two preparatory sessions lasting one to two hours each visit. The preparatory session is followed by a supervised dosing session that typically lasts 6 to 8 hours. Two therapists often staff a dosing session. Following the dosing sessions, at least two integration sessions occur to process the events of the psychedelic experience. Taken together, this structure provides 10 to 20 or more hours of guided therapeutic support per treatment course. Separate meta-analytic work shows that the length of preparation and integration directly influences the antidepressant effect size; longer supportive contact is associated with larger HAM-D drops [9]. Studying the drug in isolation is rare and ethically difficult.

By contrast, the 16 open-label TAD trials pulled from the Cipriani dataset relied on routine prescribing visits, often just 15–30 minutes per month or even less after the first consultation, with no manualized psychotherapy, no emphasis on therapeutic alliance, and no optimization of set and setting [6]. A good share of PAT's observed benefit almost certainly comes from the non-drug elements: alliance, ritualized ceremonies and behaviors, and deep psychological processing. However, the analysis labels everything "therapy" without separating the pieces.

If psychotherapy accounts for most of the benefit in psychedelic-assisted psychotherapy, then the psychedelic itself may serve mainly as an expectancy booster or catalyst. If the psychedelic compound only facilitates therapy, this raises legitimate questions about cost, scalability, and resource demands. Two therapists for six to eight hours is a significant commitment. At the same time, active-placebo trials and mechanistic imaging data indicate that 5-HT2A agonism produces specific neuroplastic changes and alters the default-mode network beyond those observed with therapy alone [10]. The current study design cannot separate these different contributions. In low-resource clinics or for patients who prefer lighter support, a purely pharmacological comparison might undervalue PAT. In high-support environments, the opposite could occur, leading to overvaluation of the intervention.

The practical stakes are considerable. Future regulatory filings will need to demonstrate real added value over existing treatments. If the observed equivalence between TAD and PAT depends largely on therapy intensity, payers may hesitate when faced with PAT's infrastructure requirements. From a clinical standpoint, patients may credit the molecule itself when the integration sessions actually did most of the heavy lifting. Upcoming trials should test PAT head-to-head against intensive psychotherapy plus open-label TAD (or therapy alone) to clear up this confound. The paper's decision not to quantify psychotherapy dose, despite citing the exact PAT protocols elsewhere, weakens its claim of truly "equal unblinding conditions."

MDD vs. TRD

PAT studies disproportionately recruit treatment-resistant depression (TRD) patients who have already failed two or more antidepressants. The COMPASS Pathways phase-2 trial [11], the NEJM single-dose psilocybin study for TRD [7], and many ayahuasca/DMT protocols all fit this pattern [12]. The authors acknowledge it: "PAT trials often TRD-focused; TADs not." Baseline depression severity was slightly lower in the PAT group (HAM-D 21.3 vs. 22.7), but models adjusted for this difference. Sensitivity analyses that dropped TRD subsets reportedly kept the null result.

This distinction matters. TRD carries a worse outlook, higher comorbidity load (even when anxiety was permitted), longer illness duration, and greater functional impairment according to STAR*D findings [13]. Reaching statistical equivalence in a harder-to-treat population could actually speak to PAT's relative strength, an angle the paper largely sets aside, instead presenting the data as "no more effective." The core issue is not the severity of the depressive episodes but rather the degree of refractoriness that depressed patients experience. A severe episode that responds robustly to a TAD is not the same as a moderate to severe episode that has shown little or no response to prior TADs. TRD patients often arrive at PAT with heightened hope for a novel breakthrough.

Some PAT protocols explicitly allowed comorbid anxiety conditions. TAD trials excluded it. This reflects real-world complexity. In severe chronic TRD that has not responded to daily pills, sexual side effects, weight gain, or adherence problems often become major concerns. Similar conclusions to the aforementioned escitalopram vs. psilocybin study would apply, in which statistical parity on the HAM-D would favor PAT. One or two sessions of PAT could replace lifelong TADs. PAT samples tend to be more educated and less racially and ethnically diverse. These factors are known to shape expectancy and alliance. The authors identify these benefits but do little else to elucidate these interactions. TRD is also highly comorbid with PTSD [14] and other conditions that may respond differently to rapid interventions.

Clinicians working with TRD should therefore avoid reading "no superiority" as blanket equivalence. The reverse may be closer to the truth. Clinicians and regulatory bodies risk drawing overly broad conclusions that overlook subgroups where PAT excels, such as patients with TRD. A recent 2026 TRD psilocybin data showed exploratory secondary benefits in remission and function. This occurred despite a non-significant primary HAM-D result. These findings remind us that raw score change alone misses the recovery markers most relevant to resistant illness [15].

Psychedelics and Psychedelic Adjacent Compounds

The PAT arm rests on only eight varied trials spanning psilocybin, ayahuasca/DMT, LSD, and MDMA; single versus repeated dosing; and differing psychotherapy protocols. Mechanistic differences exist between the compounds. 5-HT2A agonism works differently from other pathways used in the pharmacologic treatment of depression. Variable session fidelity adds more spread to the data. Heterogeneity statistics indicate an ICC of approximately 0.36 in the primary model, suggesting meaningful variability. Random-effects pooling still treats the trials as a single combined value, which, given variability, can amplify errors. Converting MADRS, QIDS, and BDI scores to HAM-D-17 introduces measurement error. As has been shown in other psychedelic studies, such measures like the QIDS may not be as reliable a measurement indicator. The conservative correlation assumption helps reduce bias, yet it cannot eliminate the error [8].

Timing differences stand out sharply. PAT primary endpoints occurred, on average, 3.4 weeks after one or two doses. This captures the rapid onset of PAT effects. Conversely, TAD endpoints averaged 8.1 weeks of daily dosing. The shorter PAT window might understate durability compared to TAD. It could also favor rapid-effect bias, but without a longer follow-up window for PAT, it is difficult to determine if one or both conclusions are true. The paper notes this point but suggests it favors PAT. That interpretation remains open to debate. This is especially true if benefits fade over time. The comparison relies on decades of historical TAD metadata drawn from trials with changing standards. This carries real risks of publication bias. The search used only PubMed and left out gray literature. Strict eligibility criteria may have led to results tending toward the null. Single-dose PAT durability lasts months in some follow-up data [16]. Chronic TAD adherence problems receive no attention. The design gives snapshots rather than long-term trajectories.

These factors leave the conclusions vulnerable. The wide confidence interval (−1.39 to 1.98) easily accommodates clinically important differences in either direction. Bayesian estimates (for instance, only a 0.2 % probability that PAT exceeds TADs by the minimal clinically important difference of 3 points) remain model-sensitive.

Thou Doth Protest Too Much

The abstract and discussion suggest the results "argue against highly optimistic narratives. They also imply broad equivalence. However, parity in acute HAM-D change excludes several key areas. PAT benefits often emerge within days. TADs take weeks. This is the issue of rapidity.

Long-term cohorts show sustained remission without ongoing dosing. Examples include Gukasyan et al. [17]. The paper does not examine durability and only addresses it in passing.

PAT sidesteps TAD sexual dysfunction, weight gain, and withdrawal. Its acute risks involve psychological distress and rare, persistent perception changes. These risks differ, and most patients favor PAT's potential side effects over TAD's effects. No safety meta-analysis appears in the paper.

Patient-centered outcomes do not receive attenti on. These outcomes include remission rates, functional recovery on the Sheehan Disability Scale, quality of life, treatment burden, and adherence. Additionally, TRD patients frequently value the single-course convenience that PAT offers.

Subgroup utility also matters. This applies to SSRI-intolerant individuals, those with comorbid anxiety, or patients with a strong preference for non-daily options.

The paper credits 55 percent of PAT's blinded advantage to expectancy. In open-label practice, this may represent a genuine therapeutic benefit rather than an artifact. The framing echoes post-MDMA skepticism. Additional consideration should be given to the wider impact that this article and ones similar to it can have on investment or insurance willingness to cover psychedelic-based therapies. Ethically, patients deserve balanced information. PAT may not win on raw scores alone. However, PAT offers a different value proposition, which includes a lower long-term burden and a novel mechanism. Ironically, initial SSRI meta-analyses faced parallel expectancy critiques, and over time, SSRIs have matured into the standard of care for depression treatment once better comparators arrived on the market.

Lastly, on the margins of depressive care, PAT may offer significant benefit, as in palliative or end-of-life depression, rapid single-dose relief may outweigh statistical parity. Outside of the United States in global mental-health settings, group ayahuasca models can and do scale differently from two-therapist predominant protocols, offering additional treatment options in areas where TADs may be limited or inaccessible. The up-front PAT cost versus the lifelong TAD pharmacy expense goes unaddressed as well.

Conclusion

This paper should spark discussion rather than shut it down, and calls for Head-to-head RCTs comparing PAT with intensive psychotherapy plus open-label TAD should be heeded. Active-placebo designs and blinding innovations deserve additional attention, including Szigeti's self-blinding methods, which use low-dose comparators and biomarker mediation. Future meta-analyses examining durability and long-term outcomes should use functional and remission endpoints, patient-reported outcomes, and subgroup analyses. These should be TRD-specific and preference-stratified. Safety, cost-effectiveness, and real-world implementation studies remain important. Standardized reporting should cover psychotherapy duration and intensity, expectancy scales such as the Credibility/Expectancy Questionnaire, and blinding indices.

Outright dismissal is premature. Instead, rigorous comparators that do not discard promising tools for the most refractory patients are needed to reach a definitive conclusion on psychedelic compounds and their role in the treatment of psychiatric disorders.

Williams and colleagues offer a valuable methodological critique. It rightly underscores the importance of blinding integrity. Nevertheless, by placing fundamentally unequal interventions and populations under an indirect lens, the study reaches beyond its data. It suggests PAT adds no meaningful value. The mismatches in delivery, patient characteristics, heterogeneity, unmeasured outcomes, and framing make its conclusions less definitive than presented. Clinicians, regulators, and readers should weigh these results alongside direct comparisons, durability evidence, and patient-centered metrics. The paper advances the scientific conversation. It need not close doors on a treatment that may still mark genuine progress beyond lifelong pharmacotherapy for carefully selected subgroups and under optimized conditions. Future studies that embrace these nuances will best serve patients navigating the evolving terrain of depression care.

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