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Psychedelic Psychiatry

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Abstract

We are amidst a 'Renaissance' in the field of psychedelic psychiatry. For several decades, following a period of promising research, governmental barriers and regulations halted any research into the utility of these substances in psychiatry. Over the past few decades, however, we are seeing a revival of these studies due to an abundance of positive findings as well as the need for improved psychiatric treatments. Studies have established substances such as psilocybin and LSD to be effective in treating depressive disorders, sometimes even more so than current 'gold standards'. MDMA is being recognized as a powerful tool, in conjunction with psychotherapy, for addressing PTSD symptomatology. This paper will provide a brief history of the use of psychedelics in psychiatry and discuss some of the most important recent research findings.

Keywords

psychedelics, psychiatry, lsd, mescaline, psilocybin

REVIEW

Psychedelic Psychiatry

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Abstract

We are amidst a 'Renaissance' in the field of psychedelic psychiatry. For several decades, following a period of promising research, governmental barriers and regulations halted any research into the utility of these substances in psychiatry. Over the past few decades, however, we are seeing a revival of these studies due to an abundance of positive findings as well as the need for improved psychiatric treatments. Studies have established substances such as psilocybin and LSD to be effective in treating depressive disorders, sometimes even more so than current 'gold standards'. MDMA is being recognized as a powerful tool, in conjunction with psychotherapy, for addressing PTSD symptomatology. This paper will provide a brief history of the use of psychedelics in psychiatry and discuss some of the most important recent research findings.

Keywords: Psychedelics, Psychiatry, lsd, Mescaline, Psilocybin

1. Introduction

The term 'psychedelics' oftentimes evokes images of long-haired, war-protesting 'hippies' or stories of individuals believing that they can fly off of buildings. It is true that their *recreational* use was popularized in the 50s and 60s during the counter-culture movement and that one can find stories of psychedelic users making poor decisions. But, these are very narrow and rigid depictions of these substances that are largely borne of government-led pursuits to quash protests and subsequent negatively-biased media coverage.[1] Despite these barriers, we are starting to see what some refer to as a 'Renaissance'[2] in the study of psychedelics, particularly in the field of psychiatry. A deeper look at psychedelic substances' histories, stigmas, and roles in improving the state of psychiatric treatment is necessary to evolve the overall public's stance on these tools.

2. History

Substances such as psilocybin (psychoactive compound in 'magic mushrooms'), mescaline (psychoactive compound in the cactus, peyote), and DMT (psychoactive compound in the vine *Banisteriopsis caapi*) have been used for hundreds and thousands of years, usually in ritualistic contexts.[2,3] Groups such as the Mayans, Aztecs, and Olmec are often cited as utilizing these substances.[2] Many groups in Mesoamerica continue these traditions. More recently, in the West, psychedelics have been of interest due to their potential use in studying and treating mental illnesses. German psychiatrist, Emil Kraepelin, used psychedelics to 'experimentally induce psychoses'.[3] Substances such as mescaline were studied in the early 1900s due to interest in their ability to induce psychotic-like states as well as derealization and depersonalization.[3] However, modern psychedelic science really began to progress following Albert Hoffman's discovery of LSD in 1943.[4] He was a Swiss chemist working on developing cardiovascular drugs at Sandoz Pharmaceuticals. Following his accidental ingestion of LSD and his reported experience, there was a desire to further study LSD and similar substances due to the possibility that they could produce mental effects similar to those seen in psychiatric disorders. Hence the term 'psychomimetics'.[3] A large number of initial studies using psychedelics were focused on alcoholism and other

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types of addictions as well as mental status at the end-of-life.[5] These studies led to a greater understanding of serotonergic pharmacology, directly contributing to the development of many modern antidepressants.[6] Unfortunately, these studies came to a rather abrupt halt during the 1960s. While these substances were showing results of value in clinical studies, they became mainstream and were associated with social unrest and the anti-Vietnam counterculture movement.[1] Sandoz Pharmaceuticals ended their distribution of LSD and psilocybin due to "unforeseen public reaction".[3] The FDA stopped approving new studies involving the use of psychedelics but did allow ongoing ones to continue. Prior to banning psychedelic studies, the NIH had funded over 130 studies involving LSD and other substances, many with positive results.[5] The last study ended in 1976 and it was not until 1994 that another study, involving DMT, was started. Around the late 1990s, neuroimaging techniques such as PET studies began to be used to characterize the effects psychedelics had in the brain.[3,7] In the early 2000s, a group of researchers at Johns Hopkins became some of the first to obtain regulatory approval to reinitiate psychedelic research in psychedelic-naive patients. This was the start of the Johns Hopkins Center for Psychedelic and Consciousness Research, which has continued to play a major role in progressing this area of research.[8] Their 2006 study of the potential therapeutic value of a psychedelic substance marked a major milestone. This one involved the use of psilocybin in patients with OCD. While they reported marked decreases in symptoms, the group was too small for the results to be considered conclusive.[3] Since then, we have seen an increase in interest and studies into this group of chemicals, particularly in the realm of depression, anxiety, and cancer-related mental health issues.

3. Current status

Currently, a search on clinicaltrials.gov for studies on psychedelic substances including LSD, psilocybin, MDMA, or mescaline will yield over 200 active or soon-to-be active projects.[9] Many of these studies are focused on depression, addiction, and PTSD. Trials involving psychedelics have become relatively standardized, involving four phases: assessment, preparation, experience, and integration.[5] In the assessment phase, patients are evaluated to determine whether they are mentally and physically suitable for psychedelic therapy. Most trials will exclude patients with personal or family histories of psychoses or bipolar disorders, however this may not be the case for long. Patients are often required to have been off of antidepressants and other psychotropic medications due to their potential interactions with one of the primary targets of psychedelic substances, the 5HT2A receptor. In the preparation stage, patients are presented with an overview of the nature and dynamics of psychedelics, usually a day or two before administration. The potential challenges one may encounter during the experience are discussed at this time as well. The experience itself typically lasts four to 5 h depending on the substance and mode of administration. Patients are given eyeshades and a preapproved music playlist. A trained guide is present with the patient throughout the experience to reassure them they are being watched over. In some cases, verbal engagement does occur, but this is not always necessary. During the integration phase, the professional guide talks about the experience with the patient and helps them make sense of it. Oftentimes, additional talk-therapy sessions follow the experience.

4. Mechanisms of action

The ways in which psychedelic substances exert their therapeutic effects have not been fully elucidated. However, there are some major targets that have been identified. Psychedelics primarily exert their influence via 5HT2A receptor agonism at pyramidal neurons in the prefrontal cortex.[7] This action underlies the hallucinogenic effects characteristic of these substances. Other serotonergic receptors such as 1 A, 2C, 4, 5, 6, and 7, as well as dopaminergic and alpha adrenergic receptors have also been implicated. Interactions with these receptors is thought to increase prefrontal cortical activity, resulting in increases in the rates of 5HT and DA neuronal firings. This is supported by PET trials showing increased striatal dopamine levels following administration of psilocybin and LSD.[11] It is thought that psychedelic substances induce neuroplastic adaptations, such as downregulation of cortical 5HT2A receptors. In studies on antidepressants, downregulation of these receptors is a correlate of chronic effective treatment.[12]

Serotonergic modulation is also associated with increases in some neurotrophic factors such as brain-derived neurotrophic factor, BDNF, involved in neuroplasticity.[7,10] Suppressed levels of BDNF due to polymorphisms (particularly Val66Met) and/or chronic stress are highly associated with major depressive disorder. Studies on antidepressant treatments have shown SSRIs to promote BDNF expression.[13] It is, however, unclear whether BDNF

is involved in modulating the effects of antidepressant/psychedelic treatment or if it is a progression/etiological factor.

Serotonergic psychedelics exert other influences through anti-inflammatory effects. Specifically, we see suppression of TNF- after administration.[7] This, and other inflammatory markers such as IL-6 and IL-1β, are associated with addiction and mood disorders.[14]

Neuroplasticity is another potential mechanism by which psychedelics may promote a healthier mental well-being. In vivo and in vitro experiments have shown serotonergic psychedelics to increase neuritogenesis, spinogenesis, and synaptogenesis.[15] This occurs via activation of tropomyosin receptor kinase B (TrkB), mammalian target of rapamycin (mTOR), as well as 5HT2A signaling pathways. It has been shown that low-dose psilocybin increases hippocampal neurogenesis, although high-dose administration may actually decrease this process. Decreased neuroplasticity is implicated in psychiatric disorders. It is thought that chronic stress leads to excessive glutamate release which contributes to neuronal atrophy/connectivity and decreased hippocampal neurogenesis.[16] We have seen that antidepressants can reverse this to some extent.[17]

5. Safety

Some of the most common arguments against the use of psychedelic substances in any manner, especially a therapeutic one, have to do with safety. Fears regarding harmful, irreversible physiological effects or risks of addiction fuel these arguments. However, these are largely unfounded and likely stem from unfamiliarity with the substances and the research into them. There is no doubt that these substances induce a vulnerable *psychological* state in patients. But, this vulnerable state may actually underlie the ability of the substances to exert their therapeutic effects. Sometimes, when taken with other substances, in unfamiliar surroundings, or with individuals unknown to the user, a state of intense anxiety and paranoia can ensue. This is what is referred to as a 'bad trip'. To safeguard against this, there are strict protocols, as mentioned above, as to who may participate in these trials. Additionally, professionals are used to provide educational sessions, to be there with the participant throughout the experience, and to help them make sense of it afterwards.

Physiologically, the effects of psychedelics are quite mild. Although MDMA has been shown to be neurotoxic at *high* doses, there is no evidence that classical psychedelics such as LSD, psilocybin, and mescaline carry this risk.[18] The most common physiological effects include dilated pupils and moderately elevated pulse and blood pressure.[19] These effects are relatively modest and are rarely enough to cause distress in patients to the point that they cannot continue.[20] In terms of abuse and addiction, psychedelics do not impose much of a risk. They are not typically considered drugs of dependence as they are not reinforcing.[21] This is consistent with observations that these substances are not reliably self-administered in nonhuman animal studies.[22]

6. Why it matters

Psychiatric disorders are pervasive throughout the world. They do not discriminate based on gender, race, or social class. Although we do see higher rates of more severe psychiatric illness in poorer communities, and in people of color, this is largely due to lack of adequate access to care.[23] This lack of access is multifactorial and includes the stigma associated with having a psychiatric illness as well as the long-held belief that one ought to be able to 'shake it off'. Depression is a particularly major public health problem associated with huge burdens. Major depressive disorder affects more than 300 million people worldwide and is the number one cause of disability, according to the WHO.[23] The relative risk of all-cause-mortality for those with depression is 1.7 times greater than the general public.[23] It is estimated that the yearly economic burden of depression is $210B.[23] While antidepressants have presented a life-saving solution for many, even the best ones show modest efficacy and come with non-negligible side effects and high relapse rates. They often take four to six weeks to have an effect, a luxury not all can afford. Additionally, the efficacy of psychiatric medications are severely limited to due patient adherence issues. Psychedelics can achieve clinically significant results in much shorter periods of time with fewer doses. For PTSD, the first line of therapeutics involves the antidepressants sertraline and paroxetine. 40–60% of patients with PTSD do not respond to these treatments.[10] Additionally, although different types of psychotherapy are the gold standard for PTSD and other conditions, many will still fail to respond. This highlights the need for additional modes of treatments with greater efficacies, rapid onset, and those that need not rely on strict adherence.

7. Study #1: Increased global integration in the brain after psilocybin therapy for depression

Daws, R.E., Timmermann, C., Giribaldi, B. et al. Increased global integration in the brain after psilocybin therapy for depression. *Nat Med* 28, 844−851 (2022). https://doi.org/10.1038/s41591-022-01744-z.

7.1. Question

Does psilocybin offer antidepressant effects and, if so, how does its mechanism compare to those of traditional antidepressants, such as escitalopram?

7.1.1. Level of Evidence

Open-label trial - III.

Double-Blind Randomized Controlled Trial - II.

7.2. Methods

7.2.1. Open-label trial

19 participants with treatment-resistant depression were enrolled. Three individuals were excluded due to excessive head fMRI head motion. Baseline clinical assessments, the Beck Depression Inventory (emphasizes the cognitive features of depression) and resting state fMRI, were obtained. fMRI data was used to compare baseline and post-treatment brain network modularity. Participants received a 'low' 10 mg psilocybin dose and a 'high' 25 mg dose separated by one week. One day later, a second set of clinical assessments and fMRIs were obtained. Pearson correlations between post-treatment brain modularity and BDI scores were calculated at one week, three months, and six months.

7.2.2. Double-Blind Randomized Controlled Trial

59 participants with major depressive disorder were recruited. 16 were excluded due to excessive head fMRI motion, adverse effects to escitalopram, COVID lockdown, or for not taking the daily placebo capsules. Baseline clinical assessments, BDI and others, and resting state fMRI were obtained. The psilocybin arm received a 25 mg dose of psilocybin on dose day 1 (DD1), followed by three weeks of daily placebo (cellulose) capsules. Following the three weeks, they were dosed again with 25 mg psilocybin on DD2 followed by another three weeks of daily placebo capsules. The escitalopram received an inert 1 mg psilocybin dose on DD1, followed by three weeks of 10 mg escitalopram. They then received another inert 1 mg psilocybin dose on DD2 followed by three weeks of 20 mg escitalopram. After this, both arms were re-assessed and had repeat fMRIs.

7.3. Results

7.3.1. Open-label trial

Rapid, substantial, and sustained reductions in depression severity (BDI score) were seen after treatment. The baseline BDI score was 34.81. At week one, the change was −21 points, $p < 0.001$, $d = 1.78$. At six months, this remained significant with a change from baseline of −14.19 points, $p < 0.001$, $d = 1.07$. Additionally, brain network modularity was significantly reduced just one day following treatment with a mean difference of −0.29 ($p = 0.012$, $d = 0.72$). Correlations between brain modularity and BDI scores were *not* significant at one week and three months, but *were* significant at six months. Significant reductions in the default mode network, DMN, recruitment were observed (mean difference −0.54, $p = 0.009$, $d = 0.75$). Additionally, they observed an increased between-network integration between the DMN and the executive network, EN (mean difference 0.53, $p = 0.01$, $d = 0.75$), and between the DMN and salience network, SN (mean difference 0.55, $p = 0.01$, $d = 0.72$).

7.3.2. Double-Blind Randomized Controlled Trial

The reductions in BDI-measured depression severity were significantly greater in the psilocybin arm at two, four, and six weeks. Pairwise comparisons relative to baseline was −8.73 ($p = 0.002$, $d = 0.98$) at two weeks, −7.79 ($p = 0.013$, $d = 0.77$) at four weeks, and −8.78 ($p = 0.013$, $d = 0.75$) at six weeks. Brain network modularity was significantly reduced in the psilocybin arm at three weeks with a mean difference of −0.39 ($p = 0.039$, $d = 0.47$) compared to no significant change in the escitalopram arm. These decreases in brain modularity in the psilocybin arm were correlated with improvement in depression symptom severity ($r = 0.42$, $p = 0.025$, one-tailed). Changes in network flexibility were correlated with changes in BDI score. Specifically increased dynamic flexibility among the EN and SN were strongly correlated with symptom improvement at six weeks. There were no significant correlations between changes in BDI scores and changes in dynamic flexibility in the escitalopram arm.

7.4. Conclusions

7.4.1. Open-label trial

The DMN is a hierarchically supraordinate intrinsic brain network associated with introspection and self-referential thinking which is often overactive in depression. Other higher-order brain

networks like the EN and SN have also been implicated in depression. The EN and SN are associated with tasks requiring cognitive flexibility like learning and task switching. The reduction in overall brain network modularity seen at day one implies a global increase in functional connectivity between the brain's main intrinsic networks. Additionally, it suggests that these decreases in modularity are related to the long-term improvements in depression severity at six months.

7.4.2. Double-Blind Randomized Controlled Trial

Psilocybin provided a greater amount of depressive symptom relief compared with escitalopram at this trial's end points. Unlike escitalopram, psilocybin treatment resulted in increased global brain network integration, strongly associated with the improvement in depressive symptoms. *Dynamic flexibility*, a term used to describe the rate at which brain regions change their community allegiance during any given time, was significantly increased in the psilocybin arm, suggesting that its antidepressant effects are related to its ability to increase connectivity between brain regions.

Taken together, this paper supports the notion of psilocybin having antidepressant effects. It goes further and describes the unique way in which it is able to improve depressive symptoms. Depression, and other psychiatric conditions, is marked by increased brain modularity or within-network connectivity and a lack of inter-network connectivity. This correlates with the ruminative, constricted symptoms in depression. Psilocybin increases global brain integration, allowing the brain to visit a broader state space with increased communications between regions ordinarily out of community limits. Specifically, we see major changes in the DMN, EN, and SN, the areas housing the highest-density of 5HT2A receptors.

7.5. Limitations

The effects of fMRI head motion cannot be totally ruled out. Additionally, it would be helpful to collect a larger number of fMRI data as the dynamic analyses are difficult to do.

7.6. Bottom-line

Psilocybin exerts antidepressant effects likely due to an increase in inter-network connectivity, allowing the brain to break harmful and repetitive thought patterns.

8. Study #2: MDMA-assisted therapy for severe PTSD, a randomized, double-blind, placebo-controlled phase 3 study

Mitchell, J.M., Bogenschutz, M., Lilienstein, A. et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med* 27, 1025−1033 (2021). https://doi.org/10.1038/s41591-021-01336-3.

8.1. Question

Can MDMA alleviate the symptomatology of PTSD when used in conjunction with manualized therapy?

Level of Evidence: II.

8.2. Methods

Studies were done in the US, Canada, and Israel. 99 participants were ultimately included. Patients were diagnosed with severe PTSD, with a mean duration of 14.8 years. 19 of the participants had the dissociate subtype. Patients were required to go through a psychiatric medication washout. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) was used to evaluate PTSD symptoms. The Sheehan Disability Scale, SDS, was used to measure functional impairment. The Beck Depression Inventory scale was used to evaluate depressive symptoms. Suicidality was assessed using the Columbia Suicide Severity Rating Scale, C-SSRS. Patients were randomized to an MDMA arm and a placebo arm. Baseline CAPS-5 and SDS scores were obtained. Over 18 weeks, participants underwent three preparatory sessions, three experimental sessions, nine integration sessions, and four endpoint assessments. Clinical assessments were completed again following each experimental session.

8.3. Results

MDMA significantly reduced PTSD symptomatology with a mean change in CAPS-5 score between baseline and 18 weeks of −24.4 in the MDMA group versus −13.9 in the placebo group ($p < 0.0001$, $d = 0.91$). The MDMA group showed a decrease in SDS score of −3.1 vs −2.0 in the placebo group ($p = 0.0116$, $d = 0.43$). The effects seen within the MDMA group were equal among participants with comorbidities often associated with treatment resistance - alcohol use disorder, substance use disorder, trauma, etc. The MDMA group showed a greater reduction in depressive symptoms as seen

with a mean change of BDI score of −19.7 versus −10.8 in the placebo group ($p = 0.0026$, $d = 0.67$). At the end of the 18 weeks, 67% of participants in the MDMA group no longer met criteria for PTSD, compared to 32% in the placebo group. 33% of the MDMA group met the criteria for remission versus 5% in the placebo group. Suicidality within the placebo and MDMA groups were similar at baseline and did not exceed baseline throughout the study.

8.4. Conclusions

MDMA administration, alongside manualized therapy, showed a greater degree of relief from PTSD symptomatology compared to manualized therapy alone. The effect size of the difference in reduction of symptomatology between the two groups, $d = 0.91$, is one of the highest seen among other PTSD pharmacotherapy, suggesting a very strong relationship between MDMA and relief of symptoms. This is compared to the effect sizes seen in comparisons between the first-line PTSD pharmacotherapies sertraline and paroxetine versus placebo, 0.31−0.37 and 0.45−0.56, respectively. PTSD is strongly associated with excessive amygdala activity in response to fearful images/situations. The amygdala is also a site of extensive serotonergic innervation. It may be that MDMA exerts its therapeutic effect of regulating fear-based behavior by modulating serotonergic activity at this site, thus facilitating the processing and release of fear-related memories.

8.5. Limitations

The population was relatively homogenous in terms of race and ethnicity. The sample size was smaller than hoped for due to COVID lockdowns.

8.6. Bottom-line

MDMA, when used in conjunction with manualized therapy, produces significantly greater relief from PTSD symptomatology compared to manualized therapy alone.

9. Study #3: Effects of Psilocybin-assisted therapy on MDD

Davis AK, Barrett FS, May DG et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2021; 78(5):481−489. doi:10.1001/jamapsychiatry.2020.3285.

9.1. Question

Is psilocybin effective in reducing depressive symptomatology in those with moderate or severe major depressive disorder?

Level of Evidence: II.

9.2. Methods

Patients aged 21−75 with moderate to severe depression were identified. 27 participants were eligible and ultimately included. Patients could not have been actively using antidepressants (at least five half-lives before screening and four months after enrollment). Other exclusionary criteria included moderate to severe alcohol use disorder, personal or family history of psychosis, serious suicide attempts, and psychiatric hospitalizations. The primary outcome measure was the GRID-HAMD, a modified form of the Hamilton Depression Rating Scale. Secondary measure outcomes included depressive symptoms assessed by the Beck Depression Inventory, BDI, and the 9-item Patient Health Questionnaire, PHQ9. Anxiety symptoms were assessed using the Hamilton Anxiety Rating Scale. The trial was divided into an immediate treatment condition group and a delayed treatment condition group. The immediate treatment group lasted eight weeks and involved at least 18 in-person visits, including two psilocybin administration sessions. A dose of 20 mg/70 kg was used on dose day 1 (DD1) and 30 mg/70 kg was used on DD2. Dose days were separated by 1.6 weeks. Participants underwent the experimental sessions around weeks three and four and then had repeat assessments on weeks five and eight. In the delayed treatment group, repeat assessments were completed on weeks five and eight. They then received the exact same treatment as the immediate treatment group with dose days occurring around weeks 11 and 12 and repeat assessments on weeks 13 and 16.

9.3. Results

Authors observed significantly lower depression scores at weeks one and four in the immediate treatment group compared with the delayed group. Compared to baseline, the mean change in GRID-HAMD scores among the immediate treatment group was −14.9 at week five and −14.4 at week eight. In the delayed treatment group, mean changes in score were +1.3 at week five and +1.1 at week eight. These differences were statistically significant at week five ($p < 0.001$, $d = 2.5$) and at week eight ($p < 0.001$, $d = 2.6$). 71% of participants

in the immediate treatment group had a clinically significant response to the intervention, defined as 50% or greater reduction in GRID-HAMD scores, at weeks five and eight. 58% met criteria for remission, a score of seven or less, at week five and 54% at week eight.

9.4. Conclusions

Psilocybin administered in the context of psychotherapy was able to produce rapid and sustained antidepressant effects in those with moderate to severe major depressive disorder with just two administrations. The rapidity with which these effects were attained parallels that of ketamine. However, some important differences include the longer lasting effects seen with psilocybin as well as its lower potential for addiction and adverse events. These qualities directly address the weaknesses of current antidepressant treatments - time to effect, need for strict adherence, and side effect profile.

9.5. Limitations

This study employed a rather short-term follow up. Like other studies mentioned, this sample was largely homogenous, consisting of mainly white, non-hispanics. The participants in this study had relatively low risks of suicide and had moderate to severe depression. These results could be different in more acutely-suicidal patients with a higher severity depression.

9.6. Bottom-line

Psilocybin is capable of achieving quick, substantial, and sustained relief from depressive symptoms when used in conjunction with psychotherapy without the side effect profile and need for adherence seen in modern antidepressant treatments.

10. Moving forward

As previously mentioned, there are hundreds of active or soon-to-be active studies on the use of psychedelic substances in the field of psychiatry. Undeniable evidence has created a path by which these substances can actually be studied in standardized settings. There still, however, remains a stigma associated with psychedelics. With the initiation of larger randomized control studies and a *fact-based* approach to educating professionals and the public about the substances' mechanisms of action, benefits, and risks, hopefully the effects of this stigma can be mitigated. Psychiatry is a field which is gaining in interest and importance in the medical landscape. While current treatments can certainly be life-saving for many, there is room to improve. Psychedelic substances are one of the most powerful, yet under-studied, tools in our belt and may represent a major component in the evolution of psychiatry.

Conflict of interest

No conflict of interest.

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