

Therapeutics Uses of Psychedelics in patients with psychiatric disorders; A Systematic Review

Sarosh Nawaz¹, Abdulaziz Mohammed Althwanay², Esraa M. AlEdani MB Ch B³, Harleen Kaur⁴, Malik Kasapoglu⁵, Rajesh Yadavalli⁶, Ann Kashmer Yu⁷
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Abstract:

The impact of psychedelic treatment on patients suffering from psychiatric diseases like depression, anxiety, post-traumatic psychiatric disorder (PTSD), and existential distress related to cancer has become very intriguing to psychiatrists in the modern era. Serotonergic psychedelics include Lysergic acid diethylamide (LSD), psilocybin, mescaline, ayahuasca, and methylene-deoxy methamphetamine (MDMA) which act agonistically on 5-hydroxytryptamine type 2-A (5-HT_{2A}) receptors. Psychedelics produce a wide range of effects, based on varying sites of 5-HT_{2A} receptors, including changes in consciousness, perception, mood, and behaviour. Psychedelics can lead to both good and bad trips depending on the dose and environment in which it is taken. We used systematic approach by strictly following Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 guidelines. Data is extracted from pub med using mesh strategy, and from google scholar and science direct by using keywords. 10 review articles are selected by using quality appraisal tools. The purpose of this paper is to highlight the mechanism of action and role of psychedelics in patients with mental health disorders. In this review, we discussed the effective models of neurodynamical changes produced by psychedelics, and we also show that these substances can be used as a potential treatment option for psychiatric patients. Psychedelics have shown effective improvement in psychiatric diseases in many pilot studies and randomized controlled trials. There is still a debate going on about which models best suggest their role in the field of psychiatry.

Keywords: Psychedelic/ Psychotropic drugs/ Hallucinogen, Serotonin receptors, LSD, mescaline, ayahuasca, Therapeutic uses, Psychiatric Diseases/Mental health, Psychotherapy.

Introduction:

Psychedelics are the group of substances known to change the human mind, these drugs have different modes of action, Serotonergic Psychedelics, especially Lysergic acid diethylamide and psilocybin act like agonist at 5-Hydroxytryptamine type 2A (5HT_{2A}) receptors and bring their effects. But we need to understand how Psychedelic agents act on these receptors to bring their therapeutic effects to psychiatric

patients There are many types of psychedelics, also known as psychotropic drugs or hallucinogens [1,2]. Some act via serotonin receptors while others have different ways of action. Lysergic acid diethylamide (LSD) has a long history, while psilocybin (mushrooms) and 3,4 Methylene-deoxy-methamphetamine (MDMA) were discovered later but became more famous than LSD. These drugs are notorious among substance abusers which is the prime reason that scientists are reluctant to work on them and discover their therapeutic effects.

Psychiatric diseases like Depression, anxiety, post-traumatic stress disorder (PTSD), alcohol addiction, and life-threatening terminal illnesses are now affecting many people around the world. Despite all the treatment options for these drugs, people with these illnesses fail to feel better and restrict themselves to a psychiatric facility. Exploring more about the role of these drugs in the field of psychiatry could lead to the chance of these drugs becoming legal in future. Psychedelics are known to cause ecstasy, hallucinations, and positive thinking in patients using it by acting on serotonergic receptors type 5 HT_{2A} [2,3]. Albert Hoffman was the one who first discovered LSD in 1938 while working on the effects of ergot derivatives at Sandoz Pharmaceutical Company, Switzerland [4]. He found its powerful effects like mood alteration, improved cognition, and a better sense of self in 1943 which led to the possibility of the use of LSD in Psychiatry. These substances were termed "Psychedelics" by Humphery Osmond, a psychiatrist, and an author, Aldous Huxley in 1957 [5]. LSD became very famous right after its discovery.

The purpose of this paper is to highlight the therapeutic effects of LSD and other Psychedelics on the human brain. Long-term psychiatric effects like hallucinations, altered perception, and addictive potential in drug abusers. The modern discovery of the therapeutic potential of psychedelics in many psychiatric disorders has led to a general curiosity among scientists regarding the mechanism of action of these drugs. The use of psychedelics in the treatment of depressive and life-threatening disorders is revolutionary and we should be able to understand its therapeutic dosage and the neural basis of its action on serotonin and dopamine receptors. Understanding the long-term adverse effects of psychedelics or hallucinogens is essential in preventing and treating substance abuse. As a doctor,

we should know how psychedelics act on serotonergic receptors and their therapeutic uses and adverse effects in Psychiatry, which areas of the human brain are affected by them and if their repeated use cause tolerance, addiction, and drug dependence in substance abusers. Psychedelics, especially Psilocybin and MDMA are most researched in the treatment of PTSD and Addiction [6]. Phase 1 and Phase 2 trials for Psilocybin and MDMA have been done till now, but among the total number of studies on psychedelics up to 2021, MDMA and Psilocybin were the most studied [6]. However, the clinical trials for LSD are very few in this modern era.

First, we must dig into the neural dynamics of psychedelic action on serotonin receptors in various regions of the human brain, then it will help us understand their therapeutic potential in mental health disorders. In this commentary, we address the rationale of researching and reviewing the mechanism of action of serotonergic psychedelics and their role in treating treatment-resistant depression, anxiety, post-traumatic stress disorder (PTSD) [7], obsessive-compulsive disorder, substance abuse, and death anxiety related to terminal illnesses like cancer and acquired immunodeficiency syndrome [7]. Secondly, we will address the proposed models and theories of how these substances effect human brain, we will do that by using neuroimaging data from both animal and human trials, studied by many authors [8].

Methods:

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 guidelines [9].

Eligibility criteria:

The studies were selected based on Participants, Intervention, and outcome elements (PIO): Participants, Psychiatric patients, or Psychiatric patients before and after treatment; Intervention, Psychedelics, or Hallucinogens therapy; Outcome, any psychedelic-induced psychological or behavioral benefit. In addition, additional inclusion and exclusion criteria were added: Inclusion, English language, free full text, abstract, narrative, and systematic review articles.

Databases and search strategy:

The search was conducted systematically using PubMed, Google Scholar, and Science Direct databases. The last date of the search for all databases was July 25, 2023. The field search used in the process was selected based on keywords used in the previous literature and through Medical Subject Headings (Mesh). It was devised as follow:

Concept 1: Psychedelics/ Therapeutic uses OR hallucinogen OR Lysergic acid diethylamide OR Psilocybin OR MDMA OR Mescaline OR Ayahuasca OR "Psychotropic Drugs/pharmacology"[Majr] OR "Psychotropic Drugs/therapeutic use"[Majr].

Concept 2: Serotonin Receptors OR 5HT2 Receptors OR "Receptors, Serotonin/drug effects"[Majr] OR "Receptors, Serotonin/therapeutic use"[Majr]

Concept 1 AND Concept 2: (Psychedelics/ Therapeutic uses OR hallucinogen OR Lysergic acid diethylamide OR Psilocybin OR MDMA OR Mescaline OR Ayahuasca OR "Psychotropic Drugs/pharmacology"[Majr] OR "Psychotropic Drugs/therapeutic use"[Majr]) AND (Serotonin Receptors OR 5HT2 Receptors OR "Receptors, Serotonin/drug effects"[Majr] OR "Receptors, Serotonin/therapeutic use"[Majr])

The strategy was devised depending on the databases used, its detailed illustration is shown in Table 1

Results:

Records were screened based on titles and abstracts. After reading the final 23 studies, 10 papers were selected for final review after applying Quality appraisal tools. The detail and steps of the selection process is illustrated in Figure 2 [10]. Quality Appraisal tools including SANRA (a scale for the quality assessment of narrative review articles) and AMSTAR-2 (a critical appraisal tool for systematic reviews that includes randomized or non-randomized studies of healthcare interventions, or both) were applied and the articles selected on this basis are shown in table 2 [11,12].

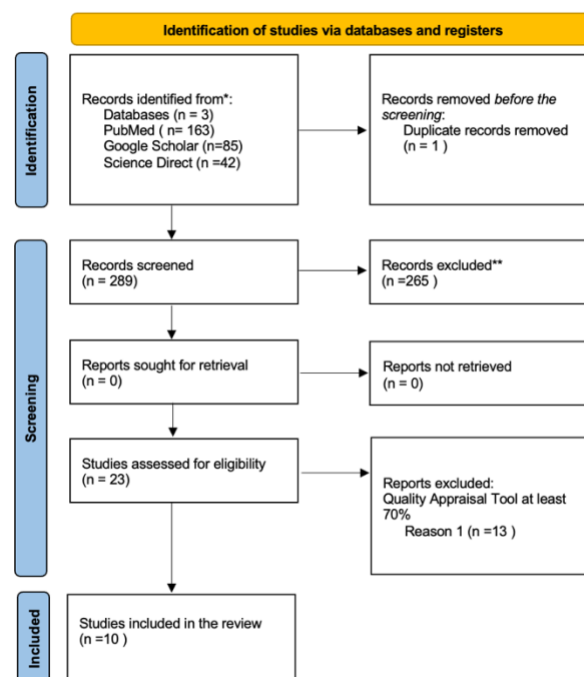


Figure 2: PRISMA flow diagram

Discussion:***History of psychedelics in psychiatry:***

Belouin and Sean reviewed the historical context of psychedelic drug research and its potential to address treatment-resistant mental health disorders. It highlights the complex history of ancient cultures, modern discovery, pop cultural movements, politics, and laws. The authors emphasize the need to overcome legal, political, and social barriers for effective research on psychedelic drug applications. It discusses psychedelic drug research, its history, use in psychiatric disorders, regulatory controls, and potential as breakthrough therapies for brain-related disorders. It highlights the discovery of LSD in the 1940s and its potential as a treatment for mental illnesses like depression, anxiety, and addiction. The authors emphasize the need for faster clinical research and more efforts to address mental illnesses and brain-related diseases. According to drug control schedules of US CSA, 1970, these drugs are classified as Schedule 1, so they cannot be prescribed freely to patients with Psychiatric Illnesses. There are limitations in psychedelic drug development due to abuse history, societal concerns, and challenges in patient safety. Additionally, strict regulatory controls from the 1960s LSD abuse hindered progress [3,13]

Psychedelic drugs are classified into stimulants and hallucinogens based on the effects they produce. But we are classifying them into two major groups based on their mechanism of action via serotonin Receptors. Because Serotonergic psychedelics are our focus in this study.

LSD, psilocybin, Ayahuasca, and Dimethyltryptamine (DMT) resemble serotonin structurally, as they all have, 6 carbon-benzene rings and a 5-sided ring with 4 carbons and 1 Nitrogen, in common. But LSD has a far more complex structure. MDMA doesn't directly stimulate 5-HT2A receptors, but it mimics the action of serotonin, which is why it is studied with serotonergic psychedelics. Mescaline and MDMA resemble dopamine and norepinephrine in structure [14].

Psychedelics and Human Brain?

The clinical uses of psychedelics have been proven by many studies, but there is little literature available regarding the mechanism of action of psychedelics. We know that any substance that enhances a person's cognition and takes them to some mystical land, must have something to do with our brain and neuronal circuits. Nutt and Spriggs et al. reviewed the literature regarding all the knowledge we have about the therapeutic role of psychedelics up to 2023. They described that the stimulation of the 5-HT2A receptor can induce altered states of consciousness, including hallucinations across sensory modalities, as well as changes in one's sense of self and other concepts. These alterations in consciousness are linked to a significant disruption of the brain cortex's electrical synchronicity,

leading to an "entropic" state characterized by decreased segregation between brain networks and increased connectivity between them [15]. They also stated that the magnitude of the psychological effects experienced during a psychedelic trip may predict the outcome of serotonin psychedelic therapy for depression.

According to James Kent, Psychedelics act mainly on neurotransmitter pathways involving Glutamate, Serotonin, Norepinephrine, Dopamine, Adrenaline, and other Amines [16]. Because of the structural similarity between these neurotransmitters and psychedelic drugs, we build the foundation that they have something to do with the neuromodulation of serotonin in the brain. The main receptors involved are Serotonin Receptors and that is mainly our focus in this commentary. Classical serotonin psychedelics like psilocybin, DMT, and LSD primarily work by stimulating the 5-HT2A receptor in the brain, resulting in their psychedelic effects. They have an agonistic effect on these receptors in Pyramidal layer V. These effects are typically blocked by 5-HT2A receptor antagonists [15]. Blocking the 5-HT2A receptors is likely to diminish the therapeutic effects of psychedelics in humans. Nutt and Spriggs et al. suggested that 5-HT2A receptor agonism disrupts the functioning of layer 5 pyramidal cells in the brain, affecting their ability to create and interpret sensory inputs and brain priors. The long-lasting positive impact of serotonin psychedelics on mood may be attributed to increased neuroplasticity, which enhances the brain's propensity for change over a short period, leading to the formation of new synaptic connections [15].

Vollenweider et al. laid out all the knowledge regarding biological mechanisms related to psychedelic experience in a paper in 2020 [14]. Nichols after reviewing the literature on psychedelic history, mechanism of action, and clinical trials from 2004 to 2016 states that the effects induced by psychedelics are greatly influenced by the user's mental expectation (set) and the environment (setting) in which they take the substances. Creating a set and setting that is conducive to a mystical experience increases the likelihood of such an occurrence, while an unorganized or party-oriented environment is less likely to result in a positive outcome[8]. They both discussed "Relaxed beliefs under psychedelics" (REBUS) and the Cortical-Striatal-Thalamic-Cortical model (CTSC) which gives an insight into how the Default Mode Network is disintegrated and other pathways including thalamus and basal ganglia show enhanced activity during a psychedelic experience. Nichols also reviewed animal studies conducted in controlled settings followed by neuroimaging which showed enhanced activity in the areas of the brain rich in 5-HT2A receptors, the principal findings documented from many studies showed:

1. Increased Visual cortex blood flow and resting state functional connectivity which accounts for altered sensory perception.

2. The disintegration of DMN and decreased resting state functional connectivity in the parahippocampus and posterior cingulate gyrus account for changes in consciousness and ego-dissolution [8]

These models were also reviewed by many other scientists including Aqil and his companions and Vollenweider himself in 2022 and 2023. Researchers have sought to enhance our understanding of psychedelic brain dynamics by examining their impact on low-level sensory areas and neural processes. For example, the study of geometric visual hallucinations has offered insights into how psychedelics influence neural activity patterns. Integrating these findings into the REBUS model to elucidate the precise mechanisms behind these effects remains a challenge. Additionally, the CTSC model, which focuses on the role of the thalamus in sensory input regulation during psychedelic experience, offers an alternative perspective. Nevertheless, it faces difficulties in explaining the specific visual alterations induced by psychedelics [14,17]. In summary, hierarchical predictive coding, the REBUS model, and the CSTC model are valuable frameworks for understanding the effects of psychedelics on the brain. However, further research and integration of domain-specific aspects of psychedelic experiences and low-level neural dynamics are needed to provide a more comprehensive explanation of these phenomena. After comparing both models we suggest that the therapeutic effects of psychedelics cannot be entirely associated with the Thalamic cortex and Basal Ganglia, but we should focus on the role of visual sensory pathways as well. There is a possibility that both high-level dimensions and low-level dimensions work in coordination via the action of psychedelics on 5HT_{2A} receptors, which are present in these areas of the brain and produce their therapeutic effect.

So, after comparing the results of all these studies we conclude that these substances stimulate some of the areas of the brain and at the same time they inhibit activity in alternate neuronal circuits. Because of this paradoxical activation and de-activation in different brain regions, psychedelics mediate their action in a complex manner, due to which the effects produced by them differ in different settings and varying doses.

Tools to identify effects of psychedelics:

Nichols mentioned 2 scales for assessment of psychedelic effects:

1. The Hallucinogen Rating Scale (HRS) was created by Strassman and colleagues in 1994 as part of their investigations into the intravenous administration of DMT.
2. The Abnormal Mental States (APZ) questionnaire, originally developed by Dittrich in 1994 and 1998, serves as another commonly employed assessment tool for quantifying the subjective effects of hallucinogens. Its primary purpose is to gauge altered states of consciousness (ASCs).

Among those two, APZ was better accepted which was further modified to lower scales and then the final one included these 11 factors to consider, which encompass the experience of unity, spiritual encounters, a sense of profound happiness, increased understanding, feeling disconnected from one's body, difficulties in controlling and thinking clearly, feelings of anxiety, intricate mental imagery, basic mental imagery, the blending of auditory and visual perceptions, and alterations in meaning (8). It was named as ACS 5-Dimensional. The Author discusses many clinical trials involving MDMA, Psilocybin, and LSD-25 using these questionnaires and Magnetic Resonance Imaging to study the response of the human brain to these substances, it all supported the fact that these drugs have agonist or partial agonist activity at 5-HT_{2A} receptors with rapid onset of action lasting for a shorter period. And LSD showed more changes than Psilocybin and DMT [8].

Aqil et al. in their paper published in 2023, mentioned the clinical studies that used questionnaires involving the Mystical Experience Questionnaire (MEQ), Altered States of Consciousness (ASC) questionnaire, and Hallucinogen Rating Scale [16].

1- ASC directly compares low-level and high-level dimensions, and when it was used it showed a positive correlation between therapeutic outcome and altered perception of sensory dimension [17].

2- MEQ is focused on mystical experiences, while the Hallucinogen rating scale only determined the correlation of perceptual alteration to remission rates when used in a study investigating the therapeutic effect of ayahuasca in patients diagnosed with depression.

Vollenweider et al. (2023) also stated the vast accepted form ACS 11-D and described it in its broader classification as:

1. Perceptual Alterations
2. Oceanic Boundlessness
3. Delusional Thinking
4. Altered Cognition
5. Auditory Hallucinations

By comparing the proportion of high and low-level dimensions in determining the mechanism of action of Psychedelics on the human brain in these questionnaires, they concluded that there should be a better tool than these to compare the role of all possible neural dimensions, including the low-level sensory circuits, that contribute to psychedelic therapeutics. After comparing these studies, we conclude that among all the modified versions of 5D ASCs, APZ, and MEQ, we must design a tool that studies all the probable effects of these psychoactive substances on the human brain [17].

Therapeutic Role in Psychiatric Diseases:

To outline the current knowledge in the field of psychedelic therapeutics, the following studies have

contributed to a better understanding of psychedelic action.

Vollenweider et al. discussed "Psychedelics and the science of self-experience" in 2020 in a paper reviewing recent advancements in understanding the neurobiology of psychedelic substances and their potential therapeutic effects. It highlights the activation of 5-HT_{2A} receptors, modulation of neural circuits, and changes in self-experience and emotional processing. Psychedelics enhance glutamate-driven neuroplasticity, contributing to clinical trials for certain psychiatric disorders. Substance-assisted psychotherapy, which uses classic psychedelics in combination with psychotherapeutic support, has shown promising outcomes in various psychiatric disorders. Research methodologies include functional MRI, dynamic causal modeling, and Bayesian statistical inference. Limitations in neuroimaging studies on psychedelics' impact on brain network dynamics require larger studies and comparable methods. It also discusses the lack of consistency in findings on surprise responses and the need for more extensive research to understand the effects of psychedelic drugs on psychiatric disorders [14]. After reviewing the scholarly article by Vollenweider et al. and Aqil et al. we can conclude that these substances mediate their action via Cortico-striato-thalamo-cortical loops. After reviewing the post-psychedelic neuroimaging studies of the human brain, they documented that there was increased connectivity in the posterior cingulate gyrus and ventral striatum, which leads to an increased flow of information to several areas of the cortex including pre-frontal and visual cortex. Also, disinhibition in the Default Mode Network (DMN) has been observed observing the neuroimaging obtained after treating the individuals with psilocybin [14,17]

Recent pilot studies, primarily utilizing psilocybin, have shown promising results in treating various conditions. However, for psychedelic treatments to gain widespread acceptance, they must undergo rigorous randomized controlled trials (RCTs), a process that poses substantial challenges. Funding for these trials is expected to come from a mix of profit-driven commercial ventures, charitable organizations, crowdfunding, and government sources. The primary goal of RCTs is to demonstrate both safety and efficacy and if successful, this could lead to regulatory licensing and rescheduling [18].

Anxiety, Depression, PTSD And Psychedelics:

Reace and Berry et al. reviewed the existing literature on the role of psychedelics in treating symptoms of Post-Traumatic Stress Disorder (PTSD) in their article in 2022 in which they included studies from 2019 to 2021. In PTSD people have symptoms of anxiety, depression, and repeated flashbacks of traumatic events. The mainstay of its treatment is Selective Serotonin Reuptake Inhibitors, but what about patients who do not respond to those medicines and do have very serious side effects from SSRIs? The Authors state that to

improve quality of life, depressive symptoms, suicidality, and self-harm tendencies in patients with PTSD and Depression, we should consider psilocybin as the preferred treatment modality in patients who are willing to try it so that we can spare them from long-lasting therapy and adverse effects of other medications [6]. This will lead to their early discharge from Rehabilitation centres and psychiatric facilities. They also included many Phase 1 and 2 Clinical Trials in their research investigating the efficacy of MDMA and Psilocybin in patients having flashbacks and symptoms of anxiety and depression and concluded that these psychedelics when used adjuvant to psychotherapy in a cared nursing facility showed promising results in improving the symptoms of PTSD and associated flashbacks, depression, anxiety and quality of life.

According to Javidi et al., patients with PTSD are at risk of co-development of diseases like anxiety, substance abuse, alcohol dependency, major depressive disorder mania, and conduct disorder [19]. Such serious psychiatric disorders can cause debilitating problems in the life of PTSD patients. By comparing these studies, we conclude that instead of just relying on conventional treatments of Depression, anxiety, and PTSD, psychiatrists should consider psychedelics as an option for the treatment of such diseases [18].

Psychedelic assisted psychotherapy in Life-threatening terminal illnesses:

Ross S. and Agrawal M. address the rationale of "Psychedelic-assisted psychotherapy" to treat demoralization syndrome and death anxiety in patients with life-threatening medical illnesses in the paper. They reviewed the efficacy of Clinical Trials (CT) and Randomized controlled trials (RCT) of psychedelics on major psychiatric illnesses that are prevailing in the world: the First Wave (1950 -the mid-1970s) which was funded by the National Institute of Health, included 3 Trials:

1. The first Open-label trial in which a single dose of 100mcg of LSD is administered in 1 group and a single dose of 2 oral opioids in the other group. The results showed better short-term pain management in patients given LSD. This trial was conducted by Kast and Collins in 1964.
2. In subsequent trials, 100mcg of LSD was given to 208 terminal cancer patients, and Kast reported alleviation of pain, decreased fear of death, and decreased rate of anxiety for up to several weeks after treatment [6].

However, these studies have undefined pain assessment tools and there is a risk of Measurement bias in this study.

The Second Wave (2011-2022), includes multicentre trials on End-stage Cancer Patients, funded by Compass Pathway in Europe and US. It includes CT and RCT of psilocybin-assisted therapy in patients with cancer-

related stress, anxiety, and suicidal ideation as well as demoralization syndrome [7]. In phase 2 they included:

1. Griffith's and Grob's RCT (N=92) conducted in 2016 and 2018 showed evidence of reduced symptoms of cancer-related anxiety, depression, suicidal thoughts, and decreased remission rates achieved by a single dose of psilocybin in patients diagnosed with advanced cancer-related psychiatric and existential distress [20,21]
2. Randomized controlled trials of Psychedelic therapy in alleviating cancer pain syndromes at NYU Langone Centre for Psychedelic Medicine. They used LSD in their trial and the primary outcome showed improvement in pain and secondary outcomes included: Existential Distress (death anxiety and demoralization syndrome), Psychiatric Distress (anxiety and depression), Quality of life, Opioid sparing, and Suicide ideation [6].
3. M. Agrawal conducted a Phase 2 trial (NCT 04593563) lasting for 8 weeks in Aquilino Cancer Centre in Maryland in May 2022 in which he administered 25mg Psilocybin to a group of 30 patients. The study used the NIH Healing Experiences in All Life Stressors (HEALS) scale [22].

2 more trials were included in that review. However, the outcome of all such studies gives good evidence of effective psychotherapy in such patients but these studies have their limitations including the possibility of type 1 error because of the small sample size and they have not described the mechanism of action of psychedelics in treating cancer-related depression and fear of death.

Stephan Ross also conducted a systematic review in 2018 in which he included 10 Clinical trials (N=445) in which 6 were open-label studies (n=341) published between 1964 – 1980, among which most patients were treated with LSD, and 4 were RCTs (n=104) published between 2011 – 2016, among which most patients were treated with psilocybin. The results of both waves of studies showed evidence of improved Quality of Life (QoL) and decreased symptoms of depression on treatment with psychedelics in the population of patients with end-stage cancer-related psychiatric distress [23].

Summary of Clinical Trials from the included studies:

Rucker along with other researchers mapped out the record of 26 clinical trials done regarding psychedelics since its discovery up to 2019, discussing the key effects of psychedelics in schizophrenics, neurotics, alcoholics, and patients diagnosed with obsessive-compulsive disorder and depression [18]. The studies conducted before the prohibition of psychedelics showed efficacy and safety but they also reported worsening of psychosis in some patients with Schizophrenia, while patients with other illnesses benefited mostly with LSD,

Mescaline, and Psilocybin. However, we cannot consider those trials efficient because they had many limitations including sample size, blinding, and absence of control groups. There are fewer studies from 1970 to 2016, after the legal restrictions of its use [18], but if we conduct trials on a bigger scale in patients who have terminal illnesses and depression, in a controlled setting along with psychotherapy, we can somehow know more about these magical substances which work in mysterious ways. However, we need more understanding regarding the action of psychedelics on neuronal circuits of the human brain. According to the Multidisciplinary Association for Psychedelic Studies (MAPS), Ayahuasca is legal in many countries in South America because of its proven efficacy and promising treatment for drug addiction and dependence [24].

Chao and Hurton et al. conducted a systematic review in 2021 through which they concluded the efficacy of psychedelic-assisted psychotherapy in patients with depression, anxiety, PTSD, and mood disorders. The included studies showed enough evidence supporting the positive outcome with treatment using MDMA and Psilocybin in multiple RCTs and pilot studies. However, the sample size was 20 or fewer in most of the included primary trials and the follow-up was less than a year [25]. Nichols et al. wrote a detailed review of all the trials conducted till 2022, the relevant trials regarding mental health disorders showed significant improvement with the use of psychedelics. The results from relevant primary studies are shown in Table 3. However, the follow-up period was brief, and immediate results were documented, but the delayed outcome was not reported [26].

Adverse effects, Addiction, Tolerance:

Serotonin psychedelics do not typically lead to physical dependence or withdrawal symptoms, and there is preliminary evidence suggesting their potential for treating addictions like alcohol and tobacco [12]. Nicholos, while reviewing the literature mentioned a study from 2015, in which Suzuki and colleagues conducted a thorough literature review on the toxicities linked to NBOMes (N-Methoxybenzyl) ingestion. They found that the most frequently observed adverse reactions included agitation, which encompassed aggressiveness, as well as tachycardia and hypertension. Notably, seizures were reported in 40% of the patients included in the study. Among the 20 individual cases they reviewed, 3, equivalent to 15%, resulted in fatalities [15].

Importantly, among most of the clinical trials reported in the included studies, there were very few adverse effects reported with Psilocybin and MDMA in a controlled setting. There is a possibility that if more trials will be carried out in the future regarding the efficacy of these substances, one must conduct it in an inpatient psychiatric facility along with proper psychotherapy.

Latest Research:

Phase 1 and 2 trials on MDMA for the treatment of PTSD were conducted from 2004-2017, and Phase 3 is estimated to be completed by March 2025 [5]. The gaps in the literature highlighted by a study in 2023 include: 1) Whether psychotherapy is a necessary component for achieving positive outcomes with psychedelic therapy, and if so, which forms of psychotherapy are most effective? 2) The factors contributing to reduced responses to serotonin psychedelics in individuals taking SSRI antidepressants or other non-5-HT_{2A} blocking drugs and the implications of this for psychedelic therapy. 3) Whether non-psychedelic 5-HT_{2A} agonists can be as effective as psychedelics in treating depression in humans, despite demonstrating antidepressant-like effects in rodents. 4) The therapeutic potential of micro-dosing psychedelics without inducing full psychedelic experiences. 5) The specific parameters of the psychedelic plasticity window, whether these parameters vary among different drugs, and how this knowledge can be optimally applied in therapeutic contexts [15]. 6) the reasons why some individuals with depression experience enduring benefits from psychedelics while others do not, and whether drugs like SSRI antidepressants or lithium can delay the return of depression after psychedelic treatment.

Limitations: Our study only includes the review articles from last ten years containing data on pharmacology and psychiatry. It doesn't involve studies on treatment of alcoholic addiction and neurotic disorders. However, the review of RCTs, clinical trials and meta-analysis can present data on the efficacy of psychedelic therapy in a more precise manner.

Conclusion:

Psychedelics have always been a mystery for scientists since its accidental discovery, many have tried to explore its effects on the human brain as these substances were famous for their use in ancient cultures. Most of the literature is focused on clinical trials of psychedelics including MDMA in PTSD patients, psilocybin in alcohol and nicotine addiction, and mescaline and psilocybin in anxiety, depression, and stress related to life-threatening illnesses like cancer. The psychedelics resulted in positive outcomes following single or two doses only, which is why we should consider them as a major treatment option in psychiatric disorders because the alternative options require longer treatments and have a very worse adverse effect profile due to which most patients do not comply. This paper reflects upon the mechanism of action of psychedelics on the human brain, neurodynamic models, and the basis of their effective use in psychiatric diseases. So, it is beneficial in the way that it gathers information in one place from both pharmacologic and psychiatric perspectives. Modern pilot studies and RCTs have built the foundation for more future discoveries that may revolutionize the world of psychopharmacology. We suggest that more Randomized Controlled Trials (RCTs) should be carried

out with a larger sample size, funded by the government and the World Health Organization. This is mandatory for us to establish the safety and efficacy of psychedelic therapy in refractive psychiatric disorders. This will open doors to a world where we can give hope to psychiatric and terminally ill cancer patients that there is a medicine that may have a greater impact on their quality of life. But their safety and efficacy should also be established before legalising these drugs.

	Database & Search Strategy	Filters	Search Results	Date and time of Research
1	Pub Med Concept 1	None	134,483	04:50:17
2	Pub Med Concept 2	None	44,253	04:53:13
3	Pub Med Concept 1 AND Concept 2	None	6,708	04:54:38
4	Pub Med	Abstract, Free full text, Full text, Clinical Trial, Randomized Controlled Trial, Review, Systematic Review, in the last 10 years	163	04:59:28
5	Google Scholar using keywords (psychedelics/ LSD, Therapeutic Action, Serotonin Receptors)	2013 - 2023 Free full text, Reviews, Systematic reviews	3090 85	3:52:50
6	Science Direct using keywords (psychedelics/Hallucinogen, Psychotherapy and Mental Health)	Free full text, Reviews, Systematic reviews from 2013 - 2023	1909 42	5:30:15

TABLE 1: Summary of search results of all databases

Kind of Study	Quality Assessment tool	Total Score	Accepted score > 70%	Studies Accepted (YOP and author first author names)	No. of References
Narrative Review	SANRA 2 Six aspects are evaluated in an article: its significance to readers, clarity of research aims/questions, literature search description, referencing, scientific rationale, and data presentation. These aspects are scored on a scale of 0 to 2 for assessment.	12	9	2016; Nichols DE. [] 2017; Rucker <i>et al.</i> 2018; Belouin <i>et al.</i> 2020; Nichols DE <i>et al.</i> 2020; Vollenweider <i>et al.</i> 2022; Samuel A <i>et al.</i> 2022; Ross S <i>et al.</i> 2023; Nutt D. <i>et al.</i> 2023; Aqil M. <i>et al.</i>	41 113 121 88 192 31 67 35 115
Systematic Review	AMSTAR 2 Sixteen criteria were assessed for a review: (1) Whether the research questions and inclusion criteria align with PICO components; (2) Whether the review report stated if methods were established before the review and justified any protocol deviations; (3) If the review authors explained their choice of study designs; (4) Whether a comprehensive literature search strategy was used; (5) If study selection was conducted in duplicate; (6) If data extraction was performed in duplicate; (7) Whether excluded studies were listed and justifications provided; (8) If included studies were adequately described; (9) If a satisfactory technique was used to assess the risk of bias in included studies; (10) Whether funding sources for included studies were reported; (11) If meta-analysis was justified, whether appropriate statistical methods were used; (12) If meta-analysis was conducted, whether the impact of risk of bias on results was considered; (13) Whether risk of bias in individual studies was considered when interpreting results; (14) If heterogeneity was observed, whether there was a satisfactory explanation and discussion; (15) If quantitative synthesis was performed, whether publication bias was adequately investigated and discussed; (16) Whether potential conflicts of interest, including review funding, were reported. These criteria were scored as YES, NO, or Partial YES, with Partial YES counting as a point.	16	12	2021; Chao Y-S, Horton J.	32

TABLE 2: Quality Appraisal

Year + Authors	Rationale	Included Literature	Disease/ Population/	Psychedelic and its effects	Authors Conclusion
2016; Nichols D. E	To highlight: history, mechanism of action via serotonin receptors, and therapeutic role of psychedelics in psychiatry.	Clinical trials from 2004 to 2016 studied therapeutic potential, safe doses, and adverse effects. And Animal studies to understand the action of psychedelics	Healthy patients N=15 N= 16 N= 10	2mg of Psilocybin: 1- Altered time perception. 2- Effect on mood. 3- Cognition 4- Memory changes (Turton <i>et al.</i> , 2014) (27) 200ug of LSD: 1- altered perception. 2- audiovisual synesthesia 3- mystical experience (Schmid <i>et al.</i> , 2015) (28) 40-80ug of LSD: Creative imagination (Carhart-Harris <i>et al.</i> 2015) (29)	People when given these substances reported the experience as pleasant rather than psychotic. When psilocybin and LSD are administered intravenously, they lead to reductions in oscillatory power within regions of the brain's default mode network, they have agonistic action on 5HT2a receptors mainly in pre-frontal and visual cortex, Locus coeruleus, thalamus, and Ventral Tegmental Area.
2017; Rucker <i>et al.</i>	Discusses the use of psychedelics in Depression, Life-threatening illness, addiction, and psychosis before and after Schedule 1, along with legal barriers in prescribing these medications.	Total 26 clinical trials, out of which 8 are from 2014 to 2017, 2 of which are included in our review.	Recurrent Depressive disorder (N=17) Treatment-resistant Major Depressive Disorder (N=20)	2.2ml/kg Ayahuasca (0.8mg/ml DMT and 0.2mg/ml harmaline): In 3 weeks study period, significant improvement in symptoms of depression was observed. (Sapolsky <i>et al.</i> 2016) (30) 10mg & 25mg psilocybin: Significant mood elation with maximum effect observed at 5-week follow-up. (Carhart-Harris <i>et al.</i> 2017) (31)	Modern clinical trials have shown promising improvement when patients with recurrent and treatment-resistant depression are treated with Ayahuasca and Psilocybin. Although more RCTs are required to decide if these drugs should be prescribed legally to such patients.
2018; Belouin <i>et al.</i>	To highlight: Psychedelic discovery followed by its prohibition, and its use in Psychiatric and Neurologic Disorders.	Albert Hoffman's discovery, United States Controlled Substance Act 1970, Prevalence of Mental Health	Major Depressive Disorder, Anxiety Disorders, PTSD, Drug overdose deaths and Suicides	CSA Schedule 1 (C1) includes Psilocybin, LSD, DMT, and Mescaline. This means that psychiatrists cannot prescribe these medications because of the high abuse potential.	These substances should be considered a potential therapeutic option for Mental Health disorders that are not responsive to conventional treatment options.
					There should be a clear policy regarding the legal use of psychedelics because some of them have shown really promising results while used in psychiatric patients.
2020; Nichols DE <i>et al.</i>	History of psychedelic use in Psychiatry	38 Clinical trials, out of which 8 match our eligibility criteria, but some of them overlap with those in other selected articles.	Alcohol Dependence, Treatment Resistant Depression, Cancer Patients	2 sessions, 0.3mg/kg and 0.4 mg/kg of psilocybin showed abstinence and decreased craving. (Johnson <i>et al.</i> 2018) (32) 10mg and 25mg Psilocybin 7 days apart Showed marked alleviation in symptoms of depression (Carhart-Harris <i>et al.</i> 2016) [33]	Psychedelics are revolutionizing the world of psychopharmacology, and its use has shown recovery in patients having stress related to cancer, alcohol addiction, and depression. These substances have caused minimal side effects among the users and further double-blinded controlled trials can help us establish their use legally in the treatment of such illnesses.
2020; Vollenweider <i>et al.</i>	To understand the neurobiological basis of psychedelic action and its use in psychiatric diseases.	Clinical trials and REBUS model (Carhart-Harris <i>et al.</i> 2019)	Neuroendocrine changes in the human brain are the basis for the treatment of Psychiatric diseases	LSD, Psilocybin, Mescaline, and DMT result in altered emotional, sensory, and social processing and produce neuroplastic and entropic changes.	Several brain regions in the cortex and thalamus including the Default mode network, frontoparietal network, and sensory pathways undergo neurochemical changes evident on MRI, following the treatment with these agents.
2021; Chao Y-S, Horton J.	To establish the efficacy and safety of psychedelic-assisted psychotherapy	2 Systematic reviews 2 RCT and 2 safety trials were included	Depression, Anxiety, Mood Disorders, Substance use disorders or PTSD	Psilocybin and MDMA-assisted psychotherapies including manualized therapy and non-directive supports were also given and they showed improvement in symptoms of mentioned illnesses.	Primary studies and trials included in the review showed enough evidence that psychedelic-assisted psychotherapy has shown promising improvements in symptoms of mental illness. However, these do not establish the safety in terms of long-term follow-up.
2022; Samuel A <i>et al.</i>	How psychedelics help in managing anxiety, depression, and flashbacks associated with PTSD	6 Clinical Trials and Many Reviews Articles	Post-traumatic stress disorder	Psilocybin and MDMA resulted in decreased anxiety, depression, and flashbacks in patients.	These drugs show significant improvement in symptoms of PTSD, which is otherwise irresponsive to SSRI. Authors analyzed

					that in 2021 most studied drugs were MDMA (45.7%) and Psilocybin (41.4%), while there were only a few studies of LSD (2%).
2022; Ross S et al.	To establish the efficacy and safety of psychedelic-assisted psychotherapy in patients with terminal illness.	1 st and 2 nd wave of psychedelic research	Cancer-related existential distress (De-moralization syndrome) Acquired Immunodeficiency Syndrome	LSD Psilocybin + MDMA	Multiple RCTs and pilot studies reviewed regarding these drugs show significant improvement in symptoms of Depression and De-moralization syndrome associated with life-threatening diseases.
2023; Nutt D. et al.	To gather all information available, present their findings, and analyze the gaps in the literature.	Articles describing the Neuroplastic effect of psychedelics and an animal study.	Depression	LSD Psilocybin	The agonistic effect of serotonergic psychedelics on 5-HT _{2A} receptors results in disruption of layer 5 pyramidal cells which are responsible for creating imagery and interpreting sensory input. However, animal studies show the formation of new synaptic channels and increased plasticity in response to psychedelics.
2023; Aqil M. et al.	Psychedelics not only stimulate high-level dimensions, but low-level sensory dimensions must have some role to play in their therapeutic action.	Studies focused on the REBUS model and CSTC model of psychedelic action and Questionnaires to assess the response of the human brain to psychedelics.	Neurodynamical changes in the human brain [Carhart-Harris et al; 2019] [34]	LSD	The subjective experience caused by psychedelics should be attributed to both High-level and Low-level Dimensions of 11-D ASC. There is a correlation between Default Mode Network (DMN) high-level processing and visual cortex low-level sensory processing.

TABLE 3: Overview of representative studies**References:**

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1. Sarosh Nawaz MBBS

sarosh.nawaz@hotmail.com
Department of Psychiatry, California Institute of
Behavioural Neurosciences and Psychology, Fairfield,
USA.

2. Abdulaziz Mohammed Althwanay

Imam Abdulrahman Bin Faisal University

3. Esraa M. AlEdani MB Ch B

Department of Internal medicine, California Institute of
Behavioural Neurosciences and Psychology, Fairfield,
USA.

4. Harleen Kaur

Department of Internal medicine, California Institute of
Behavioural Neurosciences and Psychology, Fairfield,
USA.

5. Malik Kasapoglu

California Institute of Behavioural Neurosciences and
Psychology, Fairfield, USA.

6. Rajesh Yadavalli MBBS

Department of Internal medicine, California Institute of
Behavioural Neurosciences and Psychology, Fairfield,
USA.

7. Ann Kashmer Yu

Department of Internal medicine, California Institute of
Behavioural Neurosciences and Psychology, Fairfield,
USA.