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Neuropharmacological Mechanisms of Psychedelics: Advancing Treatment Strategies for Mental Health Disorders

Vaishali G. Mundhe[1,*], Priya S. Daingade[1], Pranjali D. Ugale[1],. Kiran P. Bhosale[1], Tushar T. Shelke[2], Poonam Ingle[3], Sakshi Mehetre[3], Pratiksha Pawar[3]

Abstract

The resurgence of interest in the therapeutic potential of psychedelic drugs has caused a major upheaval in the field of psychiatry in recent years. This review's main goal is to thoroughly examine the possible benefits of psychedelic drugs in the field of psychiatry, with a focus on how they might be used as psychotherapy aids. Given their widespread use in therapeutic settings, clinical trials involving MDMA, psilocybin, ketamine, and LSD were of special interest. According to a study, these psychedelic drugs could be used in conjunction with different types of therapy to safely and effectively treat major depressive disorder (MMD), obsessive compulsive disorder (OCD), PTSD and comorbid conditions, depression and anxiety in life-threatening diseases, and various substance use disorders. In conclusion, this study shows that psychedelic drugs have therapeutic promise in psychotherapy and can be used safely and effectively to treat a variety of mental health conditions.

Keywords: Psychedelics, Hallucinogenic Drugs, MDMA, Psilocybin, Ketamine

INTRODUCTION

A pandemic of mental health disorders has spread over the world, impacting around 350 million people. A person's ideas, feelings, and behaviors can all be affected by these kinds of diseases. The focus of this review will be on common mental health conditions, such as depression, generalised anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. Although almost everyone has some of these diseases' symptoms at some point in their lives, they are only identified as mental health disorders when they start to cause ongoing problems in a person's daily activities, relationships, and career. Unlike many physical diseases and disorders, mental health issues are still poorly understood. Research has shown that mental illnesses are thought to be caused by a combination of genetic and environmental factors [1].

***Author for Correspondence**
Vaishali G. Mundhe
E-mail: mundhevaishali0721@gmail.com

[1]Department of Pharmaceutics, Genba Sopanrao Moze College of Pharmacy, Baif Rd, Wagholi, Pune, Maharashtra, India.
[2]Department of Pharmacology, Genba Sopanrao Moze College of Pharmacy, Baif Rd, Wagholi, Pune, Maharashtra, India.

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Even while mental health disorders can be inherited as parents pass on their DNA to their children, stressful lifestyles, poverty, lack of money, abuse, and other variables can significantly correlate with the development of mental health issues in an individual. Because there are so many risk factors linked to these disorders, it is difficult for researchers, physicians, and psychologists to pinpoint their exact origins and symptoms. Unfortunately, the issue is becoming worse due to the unclear understanding in this field. The minds of several people in the United States and all around the world are clearly being negatively impacted. With a variety of adverse effects and rising resistance to the available medications and treatments, treating these conditions has become more difficult.

Antidepressants, mood stabilizers, anti-anxiety medicines, and other prescription drugs are available to treat mental diseases. Patients are frequently deemed treatment-resistant since they are resistant to these drugs as expected. [2] For individuals who already don't feel like their own health, this can be an extremely unpleasant experience because they have to go through a process of elimination with multiple medications that may have unwanted side effects. Individual or group therapy is another popular treatment for mental health issues, and it's frequently combined with medicine. In these situations, a qualified therapist may discuss issues, emotions, and behaviours with a patient and offer suggestions for constructive responses or ways of thinking in other contexts. Researchers are currently investigating alternate approaches to managing mental health illnesses because of a pattern of resistance and insufficient treatment. Particularly, there has been increasing evidence that the use of various hallucinogenic drugs in different ways can help with mental health conditions such obsessive-compulsive disorder, major depressive disorder, post-traumatic stress disorder, and generalized anxiety disorder [3].

Psychedelics are mind-altering drugs that have been used therapeutically for a long time. They enable users to experience altered states of consciousness and see the world in new ways. The term "classical psychedelics" refers to a wide range of substances that mainly impact serotonin (5-HT2A) receptors in the brain.

A class of drugs known as hallucinogenic drugs, or psychedelics (Greek: "mind manifesting"), cause a range of (often profound) psychological effects that are characterized by altered states of perception, thoughts, feelings, and consciousness. Clinical research on psychedelics has been resurgent since the early 2000s, and patients and clinicians are becoming more interested in using these drugs to treat psychological conditions [4].

MENTAL HEALTH DISORDER

Major Depressive Disorder

A common yet dangerous mental illness that has an adverse effect on a person's thoughts, feelings, and behaviours is major depressive disorder (MDD). Prolonged depression, disinterest in once-enjoyed hobbies, disturbed sleep patterns, difficulty concentrating, suicidal thoughts, and more are typical symptoms. These symptoms frequently impair a person's capacity to carry out everyday tasks, relationships, education, and employment. A person must continuously exhibit one or more of these symptoms for at least two weeks, causing discernible behavioural abnormalities and deficits, in order to be diagnosed with MDD [5].

For instance, there is a 40% probability that someone who has inherited the gene that causes depression would also develop the illness if a parent or sibling has been diagnosed with it. Furthermore, the other identical twin has a 70% risk of getting MDD at some time in their lives if the first twin has the disorder. These figures unequivocally demonstrate that MDD has some heredity and gene dependence. It has also been demonstrated that a number of environmental factors influence a person's likelihood of experiencing depression at some point in their life. There is proof that a person's genetic makeup affects their risk of acquiring MDD.

For example, there is a 40% probability that someone who has inherited the gene that causes depression would also develop the illness if a parent or sibling has been diagnosed with it. Furthermore, the other identical twin has a 70% risk of getting MDD at some time in their lives if the first twin has the disorder. These figures unequivocally demonstrate that MDD has some heredity and gene dependence. It has also been demonstrated that a number of environmental factors influence a person's likelihood of experiencing depression at some point in their life. A person is significantly more likely to suffer from moderate to severe depression that interferes with their life if they have ever been a recipient of trauma, such as abuse, neglect, or assault. Another prevalent and serious risk factor for the onset of MDD is poverty. According to statistics, there is an inverse association between income and depression, suggesting that people who are poor or in a lower income category are more likely to struggle with depression. Minor complaints, such as demanding jobs and lifestyles, may also contribute to the disorder's development [6].

One of the easiest mental health issues to address is depression. A clinical interview and physical examination are usually performed by a psychologist or psychiatrist to diagnose Major Depressive Disorder (MDD). Blood tests may also be ordered to rule out other medical conditions, such as vitamin deficiencies or thyroid problems, that may be contributing to depressive symptoms. As first therapies, drugs such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed. However, about half of individuals with MDD do not respond to these medications. Additionally, research shows that 42% of patients discontinue antidepressants within the first month, and 72% stop taking them within three months. Both SSRIs and SNRIs function by blocking the reabsorption of specific neurotransmitters in the brain. Neurotransmitters are chemical messengers released by nerve cells, and after being released, they are often reabsorbed by the same cells. These medications prevent that reuptake process, allowing the neurotransmitters to remain longer between nerve cells, thereby enhancing communication. Unlike sedatives or stimulants, antidepressants influence brain chemistry without causing sedation or overstimulation [7].

Psychotherapy is frequently used alongside antidepressant medication in the treatment of depression. This often takes the familiar form of one-on-one sessions between a patient and a therapist. A widely used method is Cognitive Behavioural Therapy (CBT), which helps individuals recognize and challenge negative thought patterns, aiming to replace them with more constructive responses. CBT is designed to assess, question, and reshape harmful beliefs—a process known as cognitive restructuring. Therapists guide patients in developing healthier coping strategies and assign tasks or goals to work on between sessions. Other therapeutic approaches, such as group therapy and social skills training, have also been shown to alleviate depressive symptoms and assist individuals in managing their condition more effectively.

In cases where patients do not respond to medication or psychotherapy, psychiatrists may suggest Electroconvulsive Therapy (ECT). This treatment involves sending controlled electrical impulses to the scalp to influence brain activity. ECT has a wide range of reported remission rates, from 20% to 80%, depending on how it is administered. However, it can lead to serious side effects, such as retrograde amnesia, where the individual may lose memories from months or even years prior to the treatment. These challenges highlight the need for continued research to improve depression treatments and outcomes for those affected [8].

Post-Traumatic Stress Disorder

The condition known as post-traumatic stress disorder (PTSD) is brought on by being exposed to a stressful or detrimental incident that changes one's life. This traumatic event is frequently linked to experiencing loss following a natural disaster, sexual assault, battle in the military, or other potentially fatal situations. Although PTSD can strike at any age, the above-mentioned awareness or involvement in a stressful experience is necessary for diagnosis. As a result, the person did not necessarily need to be present at the time of the incident; hence, someone who has been exposed to hearing about certain traumatic or personal experiences on a regular basis may suffer from PTSD.

Depending on what happened, the person may avoid circumstances that could remind them of the trauma and experience dreams or flashbacks relating to the event. Intrusion, changes in mood and cognition, avoidance, or changes in arousal and reactivity are common signs of post-traumatic stress disorder. Thoughts that trigger memories or flashbacks from the incident, sometimes so intense that the person feels as though they are reliving it, are an example of intrusion. A person is said to have altered cognition when they begin to believe false information about other people, themselves, or the reason behind the incident. Further aggravate matters worse, they may begin to lose interest in the people and things they once appreciated. This is analogous to avoidant behaviour, which happens when someone avoids discussing the painful experience or putting themselves in situations that could set them off [6].

Days to years after the traumatic occurrence, PTSD symptoms may appear and eventually interfere with day-to-day functioning. It is estimated that one in eleven people may experience PTSD at some point in their lives. With the aid of treatment, a person experiencing pain can control their symptoms

and keep their condition from taking over their life. The most common treatment for PTSD is psychotherapy. As was already noted, one kind of psychotherapy is cognitive therapy, where a therapist address ingrained false ideas by teaching new coping mechanisms and cognitive processes.

Exposure therapy is another type of psychotherapy that is frequently utilized with PTSD sufferers. In this kind, experienced professionals use conversations or virtual reality to provide scenarios that could cause the patient to seek solace through direct coping. To lessen discomfort when recalling traumatic events, eye movement desensitization and reprocessing (EMDR) can be taught using external oscillatory stimulation, frequently with a therapist using their finger to guide the patient's eye movements. The usage of drugs such as prazosin, antidepressants, and prescriptions for anxiety medications can support PTSD treatments. According to the Mayo Clinic (2018), some studies have found that prazosin reduces PTSD-related nightmares, while other studies have found no benefit when compared to a placebo. Particularly when it comes to veterans of the armed forces, post-traumatic stress disorder is more common in our culture than the films may suggest. Although PTSD can still have a significant impact on certain categories of people, there are several more scenarios and contexts in which someone may experience this disease, supporting the notion that further study on efficient treatment approaches is necessary [9, 10].

Generalized Anxiety Disorder

Although it is significantly more serious and complex, generalized anxiety disorder (GAD) is sometimes misinterpreted as everyday tension and anxiety. With estimations as high as almost 42%, anxiety problems are frequently encountered in patients who also suffer from MDD. People with generalized anxiety disorder (GAD) experience anxiety and worry for no apparent reason. This uneasiness frequently causes disruptions in daily routines and work completion. GAD can show itself as physical symptoms like increased perspiration, twitching, or stomach issues in addition to psychological ones like difficulty focusing, restlessness, and persistent concern. Conflict in relations or families is one of the many symptoms that frequently worsen during times of crisis or elevated stress. A person must have this irrational worry for the majority of six months with three or more symptoms in order to distinguish persistent GAD from everyday stressors. The sense of helplessness that many people with GAD experience is another useful distinction. Normal anxiety is frequently linked to stressful life situations, but it is transient and can be controlled with relaxation and other easy methods that don't involve medical treatment. GAD may not be identified until maturity and is known to develop across a person's lifespan.

GAD affects 6.8 million persons in the US annually, with women far more likely to experience its effects. Although the exact etiology of GAD is unknown, it may be linked to biological variables, environmental stressors, inherited genes, and family history, as is the case with other mental health problems. Many of the previously mentioned techniques, including cognitive behavioural therapy and SSRI prescriptions, are used to treat generalized anxiety disorder. [11] For severe cases of GAD, benzodiazepines may be administered in addition to these therapies. Although the symptoms of anxiety disorders can be rapidly reduced by these tranquillizers, they usually come with a long list of adverse effects that can be just as bad as the diseases themselves. These include despair, agitation, disorientation, light-headedness, and more. Unfortunately, stopping benzodiazepines suddenly might result in withdrawal symptoms and serious dependence. Even if this drug might give GAD patients some short-term relief, the long-term consequences might exceed the short-term ease [12].

Obsessive Compulsive Disorder

Obsessive Compulsive Disorder (OCD) may be indicated by abnormal compulsions, obsessions, or both. Although it can still be detected later in life, OCD is frequently diagnosed in adolescence. The attitude that everything must be flawless, negative views about social conventions, or a fear of germs are examples of obsessions—beliefs that cause an individual to have abnormal desires or thoughts. Relationships or professional performance may suffer as a result of these compulsive emotions. On the other hand, compulsions are frequently recurring behaviours brought on by obsessions. These ritualistic

behaviours might become unmanageable and distressing for the person engaging in them. For example, someone who has obsessive concerns about microbes contaminating their lives could clean their house constantly and wash their hands excessively throughout the day. Tics, which can be either vocal or mechanical in nature, are common in OCD patients. Motor tics are physically repeated movements like jerking, blinking, or grimacing, whereas vocal tics may involve sounds like sniffing or moaning. The symptoms of OCD can be crippling when a person knows that their activity is unhealthy or unnatural yet is powerless to stop it [13].

As mentioned in the introduction to mental health disorders above, risk factors for OCD are often associated with genetics, environmental variables, past trauma, and abnormal brain functioning, even if the precise aetiology of the disorder is unknown. For OCD treatment to be successful, a patient must also be assessed for several other mental health issues. As is typically the case, psychotherapy can assist OCD sufferers manage their symptoms. One specific type of cognitive behavioural treatment that is commonly used in OCD cases is called Exposure and Response Prevention (EX/RP). This method entails exposing a patient to triggering stimuli under controlled conditions before stopping them from exhibiting the compulsive behaviours that go along with them. Walking into a room with all of the devices and lights on and then being led out without being permitted to switch off or unplug anything is an example of EX/RP. Along with psychotherapies, patients are frequently prescribed drugs such as SSRIs, which are typically administered in larger dosages to OCD sufferers than to those with other disorders. Researchers are investigating into new alternatives because conventional therapy choices for the aforementioned mental health illnesses aren't always effective at managing symptoms [14, 15].

CATEGORIZATION: [16, 17]

Psychedelic substances can be divided into four main categories based on their chemical structure and how they affect the brain:

1. Classic psychedelics, which primarily stimulate serotonin 2A (5-HT2A) receptors.
2. Empathogens or entactogens—such as 3,4-methylenedioxymethamphetamine (MDMA)—which act by both inhibiting and releasing serotonin and dopamine.
3. Dissociative anaesthetics, like ketamine, which block the N-methyl-D-aspartate (NMDA) receptor.
4. Atypical hallucinogens, which influence several different neurotransmitter systems simultaneously.

Lysergic acid diethylamide (LSD), psilocybin, a plant-derived indoleamine produced by numerous mushroom species, N, N-dimethyltryptamine (DMT), which is present in the South American sacred beverage ayahuasca, mescaline, 2,5-dimethoxy-4-iodoamphetamine (DOI), and 2,5-dimethoxy-4-bromoamphetamine (DOB) comprise the first category, referred to as classic or serotonergic psychedelics.

Tryptamines and phenethylamines are two other categories into which classic psychedelics can be separated. On the one hand, tryptamines include both naturally occurring indoleamines like psilocybin and DMT as well as synthetic substances like LSD. However, phenethylamines include compounds like mescaline, the primary hallucinogenic ingredient in peyote, san, and Peruvian flame cacti, MDMA, which has pharmacological similarities to amphetamine, and methamphetamine.

PSYCHEDELICS / HALLUCINOGENIC DRUGS FOR THE TREATMENTS OF MENTAL HEALTH DISORDERS

A particular class of pharmaceuticals known as hallucinogenic substances has the ability to alter a person's thoughts, behaviours, and perception of their five senses. A person may hallucinate—that is, feel or see things that are not actually there—if they take large enough quantities of the medications. They are typically grouped according to how they affect targets in the central nervous system, which causes brain transmission to be redirected.

Dissociative anaesthetics and serotonergic classic hallucinogens, also known as psychedelics, are two types of hallucinogenic medications. Psychedelics like psilocybin are thought to have agonistic effects on the 5-HT system, also referred to as serotonin receptors, while dissociative like ketamine are thought to

act on the glutamatergic system. Increases in serotonergic receptors can result in psychedelic experiences because these receptors are known to be involved in cognition, perception, and attention. The effects of either kind of hallucinogen might start to manifest within minutes and last for several hours or days. As with other drugs, some people choose to abuse hallucinogens and use them "recreationally." Hallucinogens are made up of a large range of distinct substances, each of which functions slightly differently from the others and most of which have a medicinal or practical purpose [18].

The majority of hallucinogenic drugs are classified as Schedule I substances under the Controlled Substances Act by the Drug Enforcement Administration (DEA). This indicates that the medications are deemed likely to be abused and have no recognized medical use in the United States. Therefore, the substances are prohibited when used recreationally as opposed to when they have a recognized medical use, such ketamine being used as an anaesthetic in an operation room. Hallucinogens are not always regarded as addictive, even though the DEA has identified many of them as having a high potential for abuse. In contrast to the sickness of addiction, a person who has used hallucinogenic drugs repeatedly will not suffer withdrawal symptoms or cravings to use them again. However, it is well recognized that hallucinogens, like many other medicines, can cause tolerance, which means that with time, a larger dosage of the drug is needed to have the same result. Many hallucinogens have no addictive properties, which makes them useful for medical study.

Although the entire extent of the harmful effects of long-term, uncontrolled psychedelic and dissociative drug usage is unknown, it is believed that they are uncommon. Persistent psychosis and hallucinogen persistent perception disorder, which are generally characterized by altered mental states and flashbacks to previous drug experiences, respectively, have been linked to classic hallucinogens. The most common issue with the use of hallucinogenic drugs is the potential for indirect effects brought on by altered mood and perception that differ from reality. For instance, someone under the influence of LSD, sometimes known as "acid," may be more prone to engage in risky behaviours like jumping from heights due to their changed state of consciousness.

Researchers are looking at the possible benefits of hallucinogenic substances for mental health conditions like the ones listed above, despite the fact that they are associated with negative connotations because of their misuse in recreational drug use. According to the description, both types of hallucinogens affect brain systems that are directly linked to the emergence of mental disorders. Depression symptoms and other impacts of mood disorders are associated with low levels of serotonin and glutamatergic metabolites; hallucinogenic medicines may be able to assist treat these diseases [19].

Ketamine

Ketamine is a synthetic drug with analgesic and anaesthetic effects that belongs to the dissociative class of hallucinogens. Ketamine is utilised as an anaesthetic in trauma scenarios and operating rooms because of this. Since the drug is a noncompetitive NMDA receptor antagonist, it can attach to a specific location on the receptor and prevent it from activating effectively (Figure 1). Dissociation and memory problems are among the psychotic symptoms that can arise when ketamine inhibits the activation of the NMDA receptor, a glutamate-gated ion channel that is specifically involved in memory formation, respiration, and movement. Ketamine use induces dissociation that includes hallucinations, confusion, extreme relaxation, and sensations referred to as "out-of-body" experiences. Depending on how it is administered, ketamine can be given orally or intravenously, and its effects can start to manifest one to thirty minutes later. Additionally, after delivery, residual effects may persist for up to a day. Ketamine's therapeutic utility is already established in many contexts and uses, despite the fact that its recreational use is prohibited due to the potentially harmful side effects that might arise from uncontrolled use [20, 21].

MDMA

MDMA, or 3,4-methylenedioxymethamphetamine as it is known in science, is the active component of the illegal substance ecstasy. Its effects, which include euphoria, increased sociability, and a generally pleasant condition, can be felt quickly after it has crossed the blood-brain barrier. It also has

a very quick absorption rate when taken into the body. Like other hallucinogenic drugs, this synthetic substance can cause the user to experience a distortion of time and environment. MDMA has been classified as a member of a different class known as entactogens, despite the fact that numerous studies and experts clarify that it has effects that are comparable to those of both stimulants and hallucinogens. Because of their ability to release serotonin and inhibit its reuptake, entactogens are frequently associated with emotions of joy, empathy, and relaxation, despite the fact that numerous pharmacological classes are closely linked in many ways (Figure 1). Furthermore, MDMA can also release oxytocin, norepinephrine, and dopamine when taken. MDMA was originally developed for medical use before it started to be marketed as a "party drug" for recreational use. Before the drug was formally classified as a Schedule I drug in the Controlled Substances Act, requiring FDA approval for additional research, a German scientist created MDMA in 1912 with the intention of creating a blood-clotting agent. This was before the drug was used in numerous psychotherapy trials in the 1960s and 1970s. Because of its distinct psychological characteristics, MDMA was extensively and widely studied in the middle to late 20th century, indicating a high potential for therapeutic effects. Current and future research may reach the same result [22, 23].

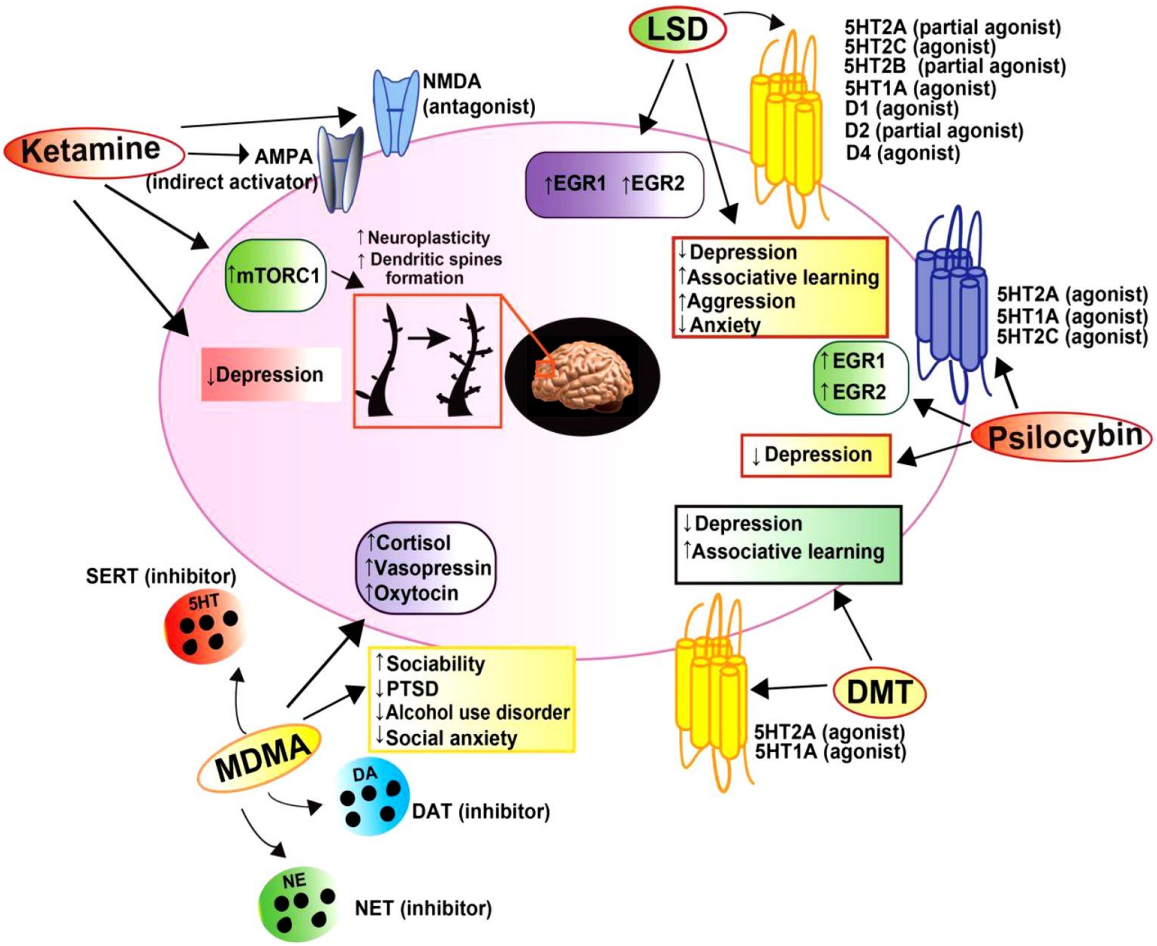

Figure 1. The physiological effects of the hallucinogenic substances LSD, MDMA, ketamine, and psilocybin as well as their targets within the body.

Psilocybin

Psilocybin is a naturally occurring drug that alters perception, cognition, and behaviour, in contrast to ketamine and MDMA. With very few negative effects, users may experience hallucinations, time and geographical distortions, enhanced creativity, strong emotions, and an overwhelming fulfilment. Kargbo goes on to say that psilocybin is regarded as a psychedelic or classic hallucinogen, which causes awareness in the hallucinatory state by activating serotonin 5-HT2A receptors (Figure 1).

"Magic mushrooms" contain psilocybin, which can be consumed and metabolised to psilocin, the primary active component with psychoactive, or mind-altering, qualities. Although it was not illegal in the US, psilocybin has historically been used extensively in spiritual events. After prolonged usage, psilocybin does not cause dependence, withdrawal symptoms, or any serious bodily side effects, making it an innocuous substance. These results have led researchers to explore the substance, which is widely referred to as "shrooms" in illicit, recreational use, as having favourable effects in psychotherapy due to the receptor's significance in the presentation of anxiety and depression [24, 25].

LSD

The adverse effects of LSD (lysergic acid diethylamide), another well-known hallucinogen, include hallucinations, distorted vision and hearing, and a euphoric sensation. LSD functions as a serotonin 5-HT2A receptor agonist, much like psilocybin, but it also binds to a number of dopamine receptors (Figure 1).

Since LSD doesn't cause severe long-term effects or withdrawal symptoms after use, it isn't typically ranked high on the list of dangerous drugs. However, if someone has a "bad trip," which is when the drug causes anxiety or unsettling hallucinations, they may be more likely to engage in risky behaviour while under the influence. In the 1930s, a Swiss chemist synthesised LSD by ingesting a portion of an ergot fungus through his skin. The primary element in LSD, lysergic acid, caused him to experience severe hallucinations and kaleidoscope-like visuals. Soon after, LSD began to appear in raves and other party settings, which resulted in its illegalisation and Schedule I authority. However, LSD's potential therapeutic benefits are acknowledged and investigated for use in psychotherapy techniques [26].

Hallucinogens are generally seen negatively as party drugs or illegal recreational activities, which prevents them from being extensively studied and approved for use in medicine. The DEA has classified these medicines as Schedule I and made them illegal due to their misuse for non-medical purposes. The drugs have been disregarded by the general public because to their recreational use, but the medical establishment has also denounced them due to certain unorthodox and dangerous research [27].

POTENTIAL TREATMENTS FOR MENTAL HEALTH DISORDERS

Research on the use of psychedelics as possible therapies for mental health issues is ground-breaking since it offers fresh therapeutic approaches to ailments that are frequently unresponsive to conventional therapies. Most prominently, the therapeutic potential of psychedelics has been investigated in relation to substance use disorders, anxiety disorders, major depressive disorder (MDD), and post-traumatic stress disorder (PTSD). This section will examine how psychedelics might be useful in treating these ailments, emphasising the ways in which they work and the findings of current clinical studies [28, 29].

Depression

The therapy of major depressive disorder (MDD), especially treatment-resistant depression (TRD), which affects those who do not respond to traditional antidepressants, is one of the most promising disciplines of psychedelic research. With quick onset and long-lasting effects after only one or two doses, psychedelics like psilocybin have demonstrated notable effectiveness in reducing depressed symptoms. This stands in stark contrast to conventional antidepressants, which may need continuous administration and take weeks to show any discernible results [30].

Mechanisms of Action

The main way that psychedelics work to reduce depression is by interacting with serotonin 5-HT2A receptors, which increases serotonin transmission and modifies brain circuits involved in mood regulation. Furthermore, by encouraging neuroplasticity, psychedelics help to reorganise preexisting brain connections and create new ones. By helping to "reset" the faulty neural networks that underpin depression symptoms, this improved neuroplasticity may provide patients a new outlook and the ability to overcome ingrained negative thought patterns.

Clinical Evidence

The potential of psilocybin-assisted therapy for the treatment of depression has been shown in recent clinical trials. According to a Johns Hopkins University study, psilocybin-treated MDD patients reported notable improvements in their depressive symptoms, with some going into remission months after starting therapy. Psilocybin was also shown to be at least as effective as a well-known antidepressant, with less side effects and longer-lasting effects, according to a study published in The New England Journal of Medicine. These results imply that psychedelics might be a good supplement or substitute for current antidepressant treatments [31].

Anxiety Disorders

The treatment of anxiety disorders, such as social anxiety disorder (SAD), generalised anxiety disorder (GAD), and anxiety associated with terminal disease, has also showed promise with psychedelics. It is thought that psychedelics' capacity to cause significant shifts in consciousness and self-perception is essential for mitigating the symptoms of anxiety [32, 33].

Mechanisms of Action

It is believed that psychedelics' ability to interfere with the default mode network (DMN), which is frequently hyperactive in people with anxiety disorders, is what causes their calming effects. Psychedelics can lessen rumination and self-referential thinking, two major causes of anxiety, by decreasing DMN activity. Additionally, psychedelic excursions' reported mystical or transcendent experiences may lessen existential worry, particularly in those with life-threatening conditions.

Clinical Evidence

The use of psychedelics to lower anxiety, especially in patients with terminal cancer, has been the subject of numerous research. A single dose of psilocybin, for example, dramatically decreased anxiety and despair in cancer patients, with benefits lasting up to six months, according to a seminal study conducted at NYU Langone Medical Centre. Anxiety was decreased as a result of participants reporting increased spiritual well-being, acceptance, and serenity. These findings imply that psychedelics may be especially helpful in treating anxiety problems that don't respond to traditional treatments [34].

Post-Traumatic Stress Disorder (PTSD)

PTSD is a crippling disorder that develops after being exposed to traumatic experiences. Cognitive behavioural therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs), two conventional therapies for PTSD, frequently offer very modest alleviation, especially for people with severe or especially persistent symptoms. MDMA (3,4methylenedioxymethamphetamine), a psychedelic, has demonstrated promise as a treatment for PTSD by promoting emotional processing and lowering the fear response linked to traumatic memories [35].

Mechanisms of Action

Despite not being a traditional psychedelic, MDMA is frequently included when talking about psychedelic therapy because it shares some pharmacological characteristics with psychedelics. Increased sentiments of trust, empathy, and emotional openness result from MDMA's promotion of serotonin, dopamine, and norepinephrine production. These benefits lessen the severity of emotional reactions and promote recovery by making it simpler for people with PTSD to face and process painful memories in a therapy context.

Clinical Evidence

The efficacy of MDMA-assisted therapy for PTSD, a topic of extensive investigation, has been demonstrated in numerous clinical trials. In a pivotal Phase 3 trial by the Multidisciplinary Association for Psychedelic Studies (MAPS), 67% of patients no longer met the diagnostic criteria for PTSD two months after receiving MDMA-assisted therapy, compared to 32% of individuals in the placebo group. The U.S. Food and Drug Administration (FDA) has designated MDMA a "Breakthrough Therapy" for PTSD as a result of these findings, highlighting its potential as a state-of-the-art therapy strategy [36].

Substance Use Disorders

Psychedelics may also have important therapeutic benefits for substance use disorders, such as alcohol, nicotine, and opiate addiction. The search for more effective approaches is prompted by the high relapse rates and poor long-term success of traditional addiction treatments [37].

Mechanisms of Action

By disrupting the ingrained thought and behaviour patterns that underlie addiction, psychedelics are supposed to aid in the treatment of substance use disorders. People may reevaluate their lives and behaviours as a result of the deep psychological insights and increased self-awareness that frequently follow psychedelic experiences, which might inspire them to make constructive changes. Furthermore, psychedelics' neuroplastic effects might help rewire the brain circuits linked to addiction, which would make it simpler for people to overcome their chemical dependence.

Clinical Evidence

There have been encouraging findings from studies on the use of psychedelics to treat addiction. According to a study from Johns Hopkins University, psilocybin-assisted therapy was successful in helping people stop smoking. The 12-month abstinence rate was 67%, which was much higher than the success rates of traditional treatments. In a similar vein, research on the traditional plant-based psychedelics ibogaine and ayahuasca has indicated promise in the treatment of opioid and alcohol addiction, respectively. These results imply that psychedelics may be essential to addiction treatment in the future, providing a fresh approach for those with substance use disorders [38].

Other Potential Applications

Psychedelics are being researched for their potential to treat a variety of other mental health diseases in addition to the ones listed above. For example, there is growing interest in using psychedelics to treat obsessive-compulsive disorder (OCD), as early research suggests that they may lessen intrusive thoughts and compulsive behaviours. Furthermore, although these topics are still understudied, some academics are looking into using psychedelics to boost creativity, increase cognitive flexibility, and advance psychological well-being in general.

Issues and Considerations: Although psychedelics have a lot of potential to help treat mental health conditions, a number of issues need to be resolved before these therapies are routinely used. Because psychedelic experiences are so strong and unpredictable, patients must be carefully screened and prepared, and experienced therapists must be present to support and lead the process. Furthermore, attaining long-lasting therapeutic results necessitates the integration of psychedelic experiences into everyday life, which calls for organised assistance and follow-up. Significant obstacles to the widespread use of psychedelics in clinical practice are also posed by legal and regulatory issues. Most governments still classify psychedelics as illegal narcotics, which restricts access to these potentially life-changing medicines, even if several have started to decriminalise or legalise them for therapeutic use. Furthermore, even while the current research appears encouraging, it is still in its early phases, making the necessity for more extensive, controlled clinical trials essential (Figure 2, 3) (Table 1) [39].

Table 1. Summary of Frequently Reported Adverse Drug Reactions.

S. N.	Drugs	Adverse drug reactions
1	Psilocybin (O-phosphoryl-4-hydroxy-N, N-dimethyltryptamine)	Dizziness, nausea, anxiety, sleepiness, hyperreflexia, moderate headache, mydriasis, and mild hypertension and tachycardia
2	LSD (lysergic acid diethylamide)	Hypophagia, lightheadedness, nausea, moderate headache, mydriasis, and mild hypertension and tachycardia
3	Ayahuasca (Banisteriopsiscaapi and Psychotriaviridis or Diplopteryscabrerana)	Mild hypertension and gastrointestinal side symptoms (diarrhoea, vomiting, and nausea) that are poorly tolerated
4	MDMA ((±)-3,4-methylenedioxymethamphetamine)	Mydriasis, tachycardia and mild hypertension, tiredness, bruxism, hypophagia, xerostomia, and overheating

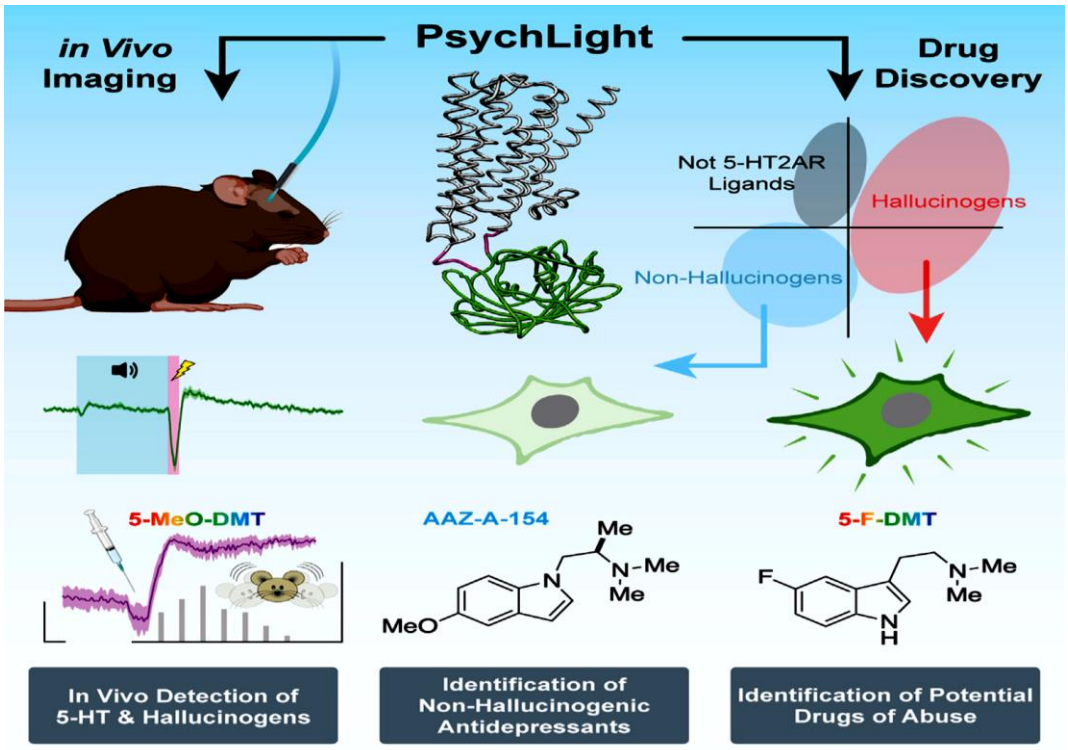

Figure 2. Engineered Psych Light: A 5-HT2AR-Based Sensor for Monitoring Serotonin Dynamics and Predicting Hallucinogenic Potential, Enabling Discovery of a Non-Hallucinogenic Antidepressant Psychedelic Analog.

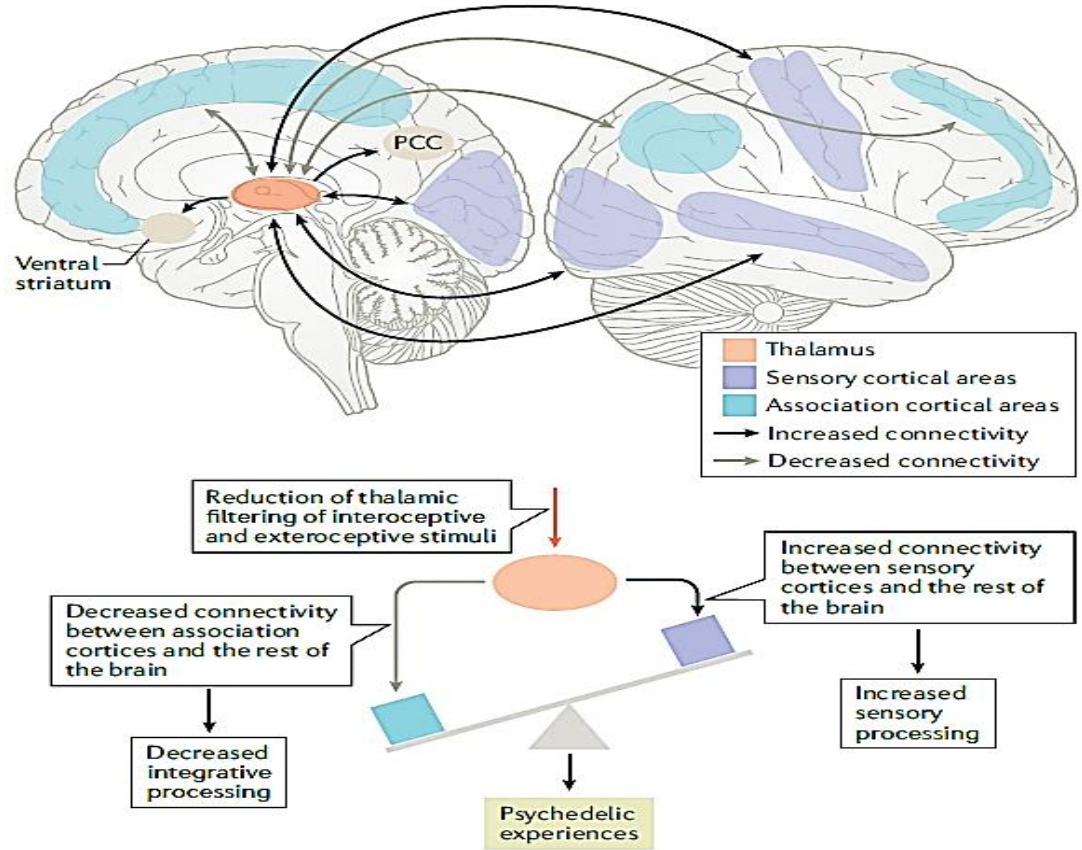

Figure 3. A Proposed Model of Psychedelic-Induced Alterations in Brain Network Connectivity.

CONCLUSION

The integration of psychedelics like MDMA, psilocybin, ketamine, and LSD with psychotherapy holds considerable potential as a safe and effective treatment strategy for various mental health conditions, including substance use disorders, PTSD, major depressive disorder, and anxiety or depression linked to life-threatening illnesses. Although clinical trial results are promising, particularly for these substances, a key limitation – such as the brief follow-up durations in ketamine studies – underscores the need for more extended and in-depth investigations. Advancing research in this field is crucial to fully realize the therapeutic value of psychedelics within contemporary psychotherapeutic frameworks.

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