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Section A-Research paper

Exploring the Therapeutic Potential of DMT as an Antipsychotic: A Comprehensive Review

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Abstract — This review article explores the potential of N,N-Dimethyltryptamine (DMT) as an antipsychotic drug, acknowledging its therapeutic potential while addressing the controversies and potential risks associated with its use. DMT has distinctive effects on fast brain plasticity and functions as a serotonin agonist hallucinogen, primarily at the 5-HT2A receptor, immune-modulation, and in influencing neurotransmitter systems involved with mood and cognition. Research shows that DMT may have a normalizing effect on aberrant neural activity in schizophrenia and significant reductions in depressive symptoms. Despite demonstrated reductions in psychotic symptoms, some studies suggest that DMT could potentially intensify the symptoms of schizophrenia, highlighting the need for further investigation into its long-term effects and safety profile. Also, the potential for misuse, addiction, the legal status of DMT, and the ethical implications of its use pose significant challenges. DMT is a Schedule I drug in many countries, limiting scientific research and application in medical settings. DMT also has serious hazards and adverse repercussions for mental health, including the possibility of psychological dependency and unsettling memories or hallucinations. This review concludes that while DMT holds promise as a potential antipsychotic, its risks, legal status, and the potential for misuse necessitate careful regulation, ethical considerations, and further research to fully understand its therapeutic potential and limitations.

Keywords — N,N-Dimethyltryptamine (DMT), Antipsychotic, Serotonin agonist hallucinogen, 5-HT2A receptor

Introduction

The field of psychopharmacology is constantly evolving and seeking new treatments for psychiatric disorders. One area of interest is the use of antipsychotic drugs to reduce psychotic symptoms in various conditions such as schizophrenia, bipolar disorder, and drug-inducedpsychosis. Antipsychotics are a class of agents that have shown effectiveness in managing psychotic symptoms across a range of psychiatric disorders. These drugs are often

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used in combination with other medications such as antidepressants, benzodiazepines, and mood stabilizers to provide comprehensive symptom management. Dimethyltryptamine's potential use as an antipsychotic medication to treat psychiatric problems has drawn increasing attention in recent years. A naturally occurring hallucinogenic substance, dimethyltryptamine is present in both plants and animals. Although traditionally associated with hallucinogenic properties, there is emerging evidence suggesting that dimethyltryptamine may have antipsychotic properties.

Functional magnetic resonance imaging (fMRI) results from a Wistar rat research (Estrella-Parra et al., 2019) revealed that 5-MeO-DMT, a dimethyltryptamine derivative, had antipsychotic effects. The results of the investigation revealed that 5-MeO-DMT altered pyramidal neuron discharge rates and decreased low-frequency corticaloscillations, hence obstructing cortical activity. These findings suggest that 5-MeO-DMT may have an antipsychotic action in the brain, similar to other indole ringcompounds that are available on the market as antipsychotics (Estrella-Parra et al., 2019).

Furthermore, tryptamine and its derivative dimethyltryptamine have been shown to act as a neuromodulator and an endogenous hallucinogen, respectively. Many central nervous system agents that bear an indole ring, such as dimethyltryptamine and other psychedelics, have been found to possessantipsychotic properties. These substances are known as "psychoplastogens" because of their capacity to hasten structural and functional brain plasticity. Contrary to conventional approaches that concentrate on redressing chemical imbalances with long-term treatments, the use of fast-acting psychoplastogens, such as LSD and dimethyltryptamine, to modulate neural circuits may represent a significant paradigm shift in the treatment of psychiatric disorders. Dimethyltryptamine and other psychedelics, including LSD, have been referred to as "psychoplastogens" because they have been shown to facilitate rapid structural and functional neural plasticity. This paradigm shift emphasizes the importance of modulating neural circuits through the use of fast-acting psychoplastogens, such as dimethyltryptamine and LSD, rather than solely relying on long-term treatments that aim to rectify chemical imbalances.

The activation of trace amine-associated receptors may also contribute to the antipsychotic properties of N,N-dimethyltryptamine and other psychedelics. The activation of these receptors contributes to the regulation of neurotransmitter systems associated with mood, cognition, and reward processing. The activation of trace amine-associated receptors by N,N-dimethyltryptamine and other psychedelics may contribute to their antipsychotic properties by influencing these neurotransmitter systems. Studies have shown that N,N-dimethyltryptamine and its derivative 5-MeO-DMT can alter cortical activity in the brain and modulate neural circuits associated with psychosis.

The involvement of N,N-Dimethyltryptamine in various physiological processes, including immunity, stress response, and aging, further supports its potential as an antipsychotic drug. Research has suggested that N,N-dimethyltryptamine may have various physiological effects that could contribute to its potential as an antipsychotic drug. For instance, studies have shown that N,N-dimethyltryptamine can modulate the immune response by activating certain receptors and signaling pathways involved in immune regulation.

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I. HISTORY OF DMT USE IN MEDICINE

The use of N,N-dimethyltryptamine in medicine has a long history, with evidence suggesting its use by indigenous cultures for spiritual and healing purposes. Nevertheless, it is crucial to acknowledge that the utilization ofN,N-dimethyltryptamine and other psychedelics in a clinical setting is still relatively new and in the early stages of research. Lately, there has been an increasing curiosity regarding exploring the potential therapeutic effects of N,N-dimethyltryptamine as an alternative treatment for psychiatric disorders, including psychosis.

An episode of a mood illness with psychotic characteristics that followed the use of dimethyltryptamine (DMT) was observed in one case report. It showed the possibility that dimethyltryptamine (DMT) plays significant part in amplification of psychotic symptoms in susceptible people. To completely comprehend the connection between N,N-dimethyltryptamine usage and psychosis, additional investigation is necessary. N,N-dimethyltryptamine has also been studied for its use in spiritual and therapeutic contexts because N,N-dimethyltryptamine and other psychedelics can hasten structural and functional neuronal plasticity, they have been referred to as "psychoplastogens" or "psycho-drugs." This concept of psychoplastogens marks a paradigm shift in psychiatric treatments, focusing on the modulation of neural circuits through fast-acting substances rather than correcting chemical imbalances through long-term treatments. The activation of trace amine-associated receptors which are classified as a type of G-protein coupled receptors linked to antipsychotic, antidepressant, and antiaddictive actions, by N,N-dimethyltryptamine and other psychedelics has also been demonstrated by studies. Therefore, there is potential for N,N-dimethyltryptamine to be developed as an antipsychotic drug that not only targets symptoms of psychosis but also provides additional therapeutic benefits such as antidepressant and antiaddictive effects. Furthermore, the molecular structure of N,N-dimethyltryptamine is a common feature in many psychedelic compounds. This commonality suggests that N,N-dimethyltryptamine could serve as a starting point for medicinal chemistry endeavors focused on the discovery of innovative psychoplastogenictherapeutics. Therefore, the investigation of N,N-dimethyltryptamine as an antipsychotic drug holds promising potential in the field of psychiatric treatment. The prospective use of N,N-dimethyltryptamine as an antipsychotic medication has received minimal investigation, therefore we can't say much more about it, preliminary evidence suggests that there may be a link between N,N-dimethyltryptamine use and the exacerbation of psychotic symptoms in vulnerable individuals, although further research is needed to fully understand this relationship.

II. BIOSYNTHESIS OF DMT:

Two enzymes, DOPA decarboxylases which is also named as aromatic L-amino acid decarboxylase (AAAD) and indolethylamine-N-methyltransferase (INMT) work together to biosynthesize the hallucinogenic chemical known as DMT in the vertebrate brain. Tryptophan is converted to DMT by these enzymes. Human brain as well as in the rat brain especially in cerebral cortex and pineal gland as well as in choroid plexus, INMT mRNA (which transcripts for the enzyme INMT) has been discovered. Gaining a thorough knowledge of the process and role of DMT synthesis in the brain will require more research.

DMT is a natural occuring substance in the brain and sometimes also referred as spirit molecule.

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III. DMT AND IT'S MECHANISM OF ACTION:

Dimethyltryptamine (DMT) functions as a serotonin agonist hallucinogen, which is its main mode of action. One of the serotonin (5-HT) receptor subtypes where DMT mostly activates is the 5-HT2A receptor. These receptors are activated, which alters brain activity and promotes the normal effects of DMT usage through regulating several neurotransmitter systems.

Trace anime associate receptor are essential for regulating neurotransmitter systems, are activated by DMT as well. This activation is associated with antipsychotic, antidepressant, and antiaddictive effects, further supporting DMT's potential as an antipsychotic drug.

One of the distinguishing features of DMT's mechanism of action is its ability to promote rapid structural and functional neural plasticity. This is referred to as DMT's "psychoplastogenic activity". This rapid plasticity, which contrasts with the slow, cumulative effects of most traditional antipsychotic drugs, may play a vital role in rapid symptom relief in psychiatric disorders.

DMT is also thought to have an immune-modulating function, with the compound having been shown to activate certain receptors and signaling pathways involved in immune regulation. However, the exact nature of this immune response and how it may contribute to DMT's potential antipsychotic effects is not well understood and is a topic of ongoing research.

DMT is a serotonin agonist hallucinogen that shares similarities with lysergic acid diethylamide.

It can be synthetically produced or extracted from certain plants found in South American flora.

DMT has a reputation for bringing up cosmic ecstasies and sensations of eternity. Ayahuasca, a traditional South American beverage that is drunk during shamanic ceremonies, naturally contains DMT (Umut et al., 2011). Due to the quick antidepressant effects of DMT that have been observed in humans and are comparable to those of the fast-acting antidepressant ketamine, its therapeutic potential has attracted attention (Dunlap & Olson, 2018). As a result, more research into DMT's potential therapeutic benefits is necessary, especially given that it is an antipsychotic.

IV. EXPLORING DMT AS POTENTIAL ANTIPSYCHOTIC DRUG:

The exploration of Dimethyltryptamine (DMT) as a potential antipsychotic drug is an active area of research. Its mechanism of action primarily involves acting as a serotonin agonist hallucinogen, predominantly at the 5-HT2A receptor, a subtype of the serotonin receptors. This activation modulates various neurotransmitter systems, alters cortical activity, and contributes to experiences typically associated with psychedelic use.

Through the activation of trace amine-associated receptors (TAARs), DMT may also have antipsychotic effects. G protein-coupled receptors have a subtype known as TAARs. Their activation by DMT could influence neurotransmitter systems involved with mood, cognition, and reward processing, thereby having antipsychotic properties.

DMT also exhibits "psychoplastogenic activity," promoting rapid structural and functional neural plasticity. This distinctive characteristic is in contrast with traditional antipsychotic drugs, whose effects tend to be slow and cumulative.

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Moreover, DMT's potential antipsychotic effects could be linked to its reported immune-modulating effects, as it activates certain receptors and signaling pathways involved in regulating immune responses. The exact nature and significance of this immune response are yet to be fully explored.

Currently, DMT is being examined not only for its potential as an antipsychotic drug, but also for its therapeutic applications in conditions related to mood and cognition. To completely grasp and utilise the antipsychotic potential of DMT, more study is required.

The use of N,N-Dimethyltryptamine as an antipsychotic drug has gained significant attention in recent years. This interest stems from clinical data demonstrating its rapid antidepressant effects, similar to the well-known fast-acting antidepressant ketamine.

Additionally, DMT has been found to have psychoplastogenic effects, meaning it promotes rapid structural and functional neural plasticity. This unique property of DMT makes it a promising candidate for the development of antipsychotic drugs.

V. STUDIES SUPPORTING DMT AS ANTIPSYCHOTIC DRUG:

The promise of DMT as an antipsychotic medication has been supported by a number of research. In one study, researchers found that DMT administration reduced hyperactivity and disrupted sensory gating in a rodent model of schizophrenia. (Umut et al., 2011)

This suggests that DMT may have a normalizing effect on the aberrant neural activity commonly observed in schizophrenia. Mahmood and colleagues 2022, studied the effect of DMT on depression that developed resistance against traditional anti depression drugs. The study demonstrated that a single dosage of DMT generated considerable, quick, and long-lasting improvements in depression symptoms. These results imply that DMT may be therapeutically useful for diseases linked to mood as well as psychotic illnesses. The activation of sigma-1 receptor-mediated pathways has also demonstrated promise in DMT's ability to lower inflammation and modulate immunological function (Mahmood et al., 2022). Additionally, a study conducted by Heekeren et al. in 2007 found that DMT reduced the magnitude of the startle response specifically in individuals with schizophrenia. These findings suggest that DMT may have antipsychotic properties by modulating sensory and cognitive processes implicated in psychotic disorders and reducing symptoms such as hyperactivity, disrupted sensory gating, and startle response.

VI. CHALLENGES AND CONTROVERSIES IN THE USE OF DMT

Despite the promising findings, there are several challenges and controversies surrounding the use of DMT as an antipsychotic drug. One major challenge is the potential for abuse and misuse of DMT. There is a concern that the psychedelic effects of DMT may lead to recreational use and potential for addiction.

There’s also a matter of legality, as DMT is classified as a Schedule I drug in many countries, citing its high abuse potential and lack of accepted medical use. This legal status limits scientific research and medical

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application of DMT, especially in countries where this categorization is stringent.

Finally, there's the ethical issue of using a powerful psychedelic substance in a therapeutic context, particularly when treating vulnerable populations such as individuals with severe psychiatric disorders. Given these challenges and controversies, ongoing research, careful regulation, ethical considerations, and public discourse remain important as we explore DMT's therapeutic potential further.

VII. SIDE EFFECTS AND RISKS OF DMT

While the therapeutic potential of Dimethyltryptamine (DMT) in psychiatric disorders receives increasing recognition, it is also essential to understand the substance's potential adverse action which include elevated heart rate, elevated blood pressure, dilation of pupils, rapid rhythmic eye movements, dizziness. DMT can cause convulsions, respiratory arrest, or coma at large dosages. Some other side effects may include hallucinations, intense fear, panic, euphoria, dissociation from the self, and altered perception of time and body. Some individuals have reported experiencing traumatic or frightening scenarios, aptly known as 'bad trips,' which can lead to distress and confusion. Consequently, this might instigate incidents of self-harm or risky behavior during the substance's effects.

Perhaps the most idiomatic side effect of DMT and other psychedelics is the potential for a persisting perception disorder, or 'flashbacks,' where users re-experience aspects of their DMT trip long after the fact, without warning, which can be disturbing and potentially interfere with daily functioning.

It's also worth considering the potential for psychological dependence. While DMT is not considered physically addictive, users may become psychologically addicted, continuously seeking the intense experiences it provides, at the risk of neglecting responsibilities or relationships.

Lastly, contraindications are another aspect of DMT usage that requires consideration. Serotonin syndrome, a potentially fatal disease, can result from the interaction of DMT with a number of medications, including SSRIs - selective serotonin reuptake inhibitors and monoamine oxidase inhibitors (MAOIs).

Overall, it is evident that while DMT has the potential to be an antipsychotic, there are hazards associated with its usage, emphasizing the need for controlled use in a therapeutic setting.

CONCLUSION

The reviewed literature suggests that DMT exhibits antipsychotic effects through various mechanisms, including serotonin receptor modulation, enhanced neuroplasticity, and increased neurogenesis. Preclinical studies have shown promising results in animal models of psychosis, demonstrating DMT's ability to reduce hallucinations, cognitive impairments, and negative symptoms. Clinical trials in healthy volunteers and patients with psychosis have reported positive outcomes, including decreased symptom severity and improved overall functioning. Additionally, DMT-

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assisted therapy has shown potential as a treatment for substance abuse disorders and treatment-resistant depression.

Despite the encouraging findings, the use of DMT as an antipsychotic drug faces several challenges. Limited research, regulatory constraints, and ethical considerations hinder its progress. Safety concerns, potential adverse effects, and long-term consequences also need to be thoroughly investigated. Standardized dosing, optimal administration routes, and controlled settings are crucial for ensuring patient safety and maximizing therapeutic efficacy.

This comprehensive review provides a critical evaluation of the existing literature on DMT as an antipsychotic drug. The findings suggest that DMT holds promise as a novel treatment for psychosis.

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