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Abstract

Psychedelic drug research has been a controversial topic throughout the past several decades. Often times, these so called "psychedelics" are associated with the counter cultural revolution of the 1960's and the subsequent war on drugs. That being said, psychedelics were not born into the counter-culture, but rather the counter-culture absorbed the drug into its anti-establishment message. The inception of psychedelic research began with Dr. Arthur Heffter, who was the first "Western" doctor to analyze the primary alkaloids in the traditional religious sacrament, Peyote cactus. Since then, much has been learned of psychedelics and their effects. Psychedelics provide deep spiritual experiences for their consumers. A psychedelic such as Lysergic Acid Diethylamide (LSD) elicits feelings of insight and epiphany. LSD can also provide feelings of connectedness and dissolution of boundaries between ones-self and the environment around them. In modern day, psychedelic research has resurged for a variety of applications including more developed techniques for understanding medical and therapeutic treatment. Psychedelics, despite the preconceived notions associated with them, could potentially offer a wide array of therapeutic uses in psychology and psychiatry. Breakthroughs with imaging techniques, along with a better understanding of the therapeutic actions of these substances, have opened the door to a more complete understanding of a complex topic. Today, psychedelic research is taking place all over the globe, and this review aims to discuss its promising clinical applications.

Key Words: Psychedelics, Neuropsychopharmacology, MDMA, Psilocybin, LSD, anxiety disorders, affect disorders, addiction

Introduction

Clinical and academic research of psychedelics has been ongoing since the 1950's, but far less frequently. With novel treatments for a variety of psychological and psychiatric disorders on the rise, psychedelics have yet again appeared on the scene. These disorders range from anxiety disorders, addiction, and affect disorders. Psychedelics were originally thought to be a key to determining schizophrenic neurobiology in the late 1950's, but the scientific view of psychedelics has shifted significantly since then.

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The sweeping prohibition of most of these "classic" psychedelics has not only made research with them much more difficult, but it left the state of research in disarray, as many trials were happening simultaneously at the time of the ban. The early nineties brought about some of the first studies involving psychedelics since that era (Strassman R., 1996). In this Literature Review, the most commonly known psychedelics and their respective clinical studies will be analyzed. Many new studies have shown a potential therapeutic effect with psychedelic treatments for the aforementioned disorders.

There are a handful of psychedelics that are being researched today for their therapeutic effect. These include 3,4 – Methylenedioxymethamphetamine (MDMA), Psilocybin, Lysergic Acid Diethlyamide (LSD), and Ibogaine (MAPS, 2016). Other psychedelic substances that are not currently undergoing clinical investigation but are and have been researched include Mescaline (primary alkaloid of the peyote cactus), ketamine, and N,N-Dimethyltryptamine. The purpose of this review is discuss the most promising research of these substances.

3,4 – Methylenedioxymethamphetamine (MDMA) and PTSD

The first psychedelic that many researchers have been examining over the past thirty years has been the drug called MDMA. 3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy for Post-Traumatic Stress Disorder (PTSD) has been an increasingly intriguing topic in research. MDMA provides feelings of euphoria and a deep connection with individuals in one's environment. Most studies primarily focus on the efficacy of MDMA as a tool within psychotherapy to increase openness in patients who have PTSD. The general view of MDMA is that it promotes deep personal connections between the consumer and the therapist (Greer and Tolbert, 1998). This is an integral part of therapy, as many PTSD patients do not feel comfortable talking with their therapists about traumatic experiences.

PTSD is a debilitating disorder in which few pharmacological treatments have proven to be efficacious. The studies done thus far have focused primarily on how MDMA can be supplemented in with psychotherapy to effectively help patients overcome their anxieties. In a preliminary study published in the Journal of Psychopharmacology by Mithoefer et al. (2010), a careful and ethical methodology had to be developed in order to properly address the safety concerns with participants. Participants who volunteered were examined by physicians and an independent rater to assess their capability to participate in the study. After the initial enrollment, subjects were randomized into a double – blind placebo experimental structure. There were two groups, one that would receive the active form of the drug (MDMA), and one that received an inactive placebo (lactose). Some studies choose a much less active form of the substance, such as a sub-perceptual dose or metabolite, but generally an inactive placebo control is preferred. This particular caveat is one to note, as patients can tell when they have received an inactive placebo (Mithoefer M., 2010). That being said, this is generally the standard for all studies using psychedelics as the primary pharmacological agent. This study showed an improvement in PTSD symptoms throughout a two-month period.

While observing the state in which MDMA research currently exists, it is easy to see that anxiety disorders are of primary concern. MDMA has a high binding affinity to serotonin (5-HT) and adrenoceptors according to Battaglia et al. (1988). It was noted in the Battaglia et al. report, that it had a similar binding affinity to citalopram, which is a common SSRI often used in PTSD treatment.

Beyond the neurobiological mechanisms, it is easy to speculate as to why MDMA would be a good candidate. Reportedly, MDMA allows patients to be more comfortable with talking about their traumatic pasts (Cami, et al., 2000, Greer & Tolbert, 2011). One of the biggest obstructions to therapy with individuals suffering from PTSD is their ability to recall events without being re-traumatized by them. A hallmark of PTSD is the reliving of traumatic experiences. Many MDMA studies seem to support the hypothesis that this drug can be used to enter a sort of goldilocks zone (Greer & Tolber, 2011). MDMA can reportedly allow patients to revisit troubling experiences and be able to discuss them in an open and connected manner with their psychotherapist with little trouble.

These results have to be measured, and a handful of screening tests have been designed to fully understand psychologically how MDMA is effective. CAPS is an interview test used to assess the symptoms of PTSD and has been widely accepted as a valid measure for quantifying these symptoms in a comparable format (Blake, D., et al. 1995). A few limitations to CAPS and other tests of this sort is that they are self-reported.

Despite the limitations, initial studies found that scores for severity of PTSD symptoms reduced when the psychotherapy was paired with MDMA. This trend is observed in other preliminary studies done on MDMA and other anxiety disorders (Bouso J. C., et al., 2008, Johansen & Krebs, 2009).

In addition to psychological studies with patients suffering from PTSD, there have been many studies in mice that give key insight into some of the neurobiological mechanisms involved in MDMA action (Cami et al., 2000, Green et al., 2003). For instance, in Nature's Journal of Neuropsychopharmacology, Dr. McGregor et al. (2003) examined the behavioral and neurobiological changes involved with MDMA. In mice, a large dose of MDMA was associated with serotonergic toxicity. This study, along with a few others (Cami et. al., 2000, Quinton S., 2006), provide the scientific community with an understanding of the possible dangers of using a drug such as MDMA in clinical settings. Currently, the Multidisciplinary Association for Psychedelic Studies (MAPS) has worked in conjunction with Dr. Mithoefer (aforementioned author) and the FDA to complete a Phase 2 pilot study for FDA indication. Their current projection as of 2015 is to complete the FDA indication trials by 2021 (MAPS Media Page, 2015).

Psilocybin and Treatment Resistant Depression

As aforementioned, MDMA is only one of many psychedelic substances being researched. There are a few substances that have a much more desirable physiological side-effect profile. For instance, psilocybin is another drug that could offer therapeutic benefit in a clinical setting but without noted neurotoxicity. Psilocybin is a pro-drug to psilocin, a serotonergic drug that binds to the 5-HT_{2A} (Jerome L., 2007) receptor acting as a partial agonist. Psilocybin differs heavily from MDMA in the sense that it creates a more distorted and hallucinogenic experience. Psilocybin has been reported to cause more creative and deep thinking about one's spiritual and personal wellbeing (Griffiths et al., 2006). Many users of the drug report sensations of insight and a spiritual enlightenment. Studies done with psilocybin investigate its potential in treating treatment-resistant depression, end of life anxiety, and addiction to stimulants.

The pharmacological profile of psilocybin is quite unique when compared to the current anti-depressant treatments available for prescription use today. Most drugs used to treat depression act on a variety of serotonin receptors to inhibit the breakdown or re-uptake of extra-cellular serotonin. In theory these drugs work to, over time, increase the levels of serotonin, thus alleviating depression that could possibly stem from serotonergic deficiencies. This technique is widely considered the best way to pharmacologically treat depression (Paykel 1993, Sclar et al., 1998). Although, considering the delayed action of these prescription drugs, which can be 4-6 weeks, there is a need for faster-action novel treatments: enter psilocybin.

A study published in the Lancet journal of Psychiatry investigated the role that psilocybin could play in therapy with treatment-resistant depression. Carhart-Harris et al. (2016), in a feasibility study, looked into the potential role for psilocybin to treat this form of depression as well as the physiological safety profile.

In the study with Dr. Carhart-Harris et al., participants were considered if they scored a seventeen or higher on the twenty-one item Hamilton Depression Rating Scale (HAM-D). This scale is a fairly accurate measure of depression, but yet again the trouble with self-reported symptoms must be take into account. In addition to this test score, patients had to have undergone at least two rounds of anti-depressant treatment to no avail. This qualified the participants as treatment-resistant and made up a group of twelve individuals. In this study, there was no control group or blinding, which could certainly detract from its findings. Even still, two sessions where psilocybin was administered in the presence of a trained psychologist occurred. The scores of depression were then measured by the mean depression severity (QIDS) over a period of three months. The scale is out of twenty-five: six to ten being mild, eleven to fifteen being moderate, and sixteen to twenty being severe depression. The study's participants all showed a significant reduction in depression scores one week following the final of the two treatments.

When looking at the way this study was designed, it is easy to understand the drawbacks regarding the small group and lack of controls. That being said, the results are thought provoking. Dr. Carhart-Harris describes it best himself:

> Because this was a small-scale feasibility study with an open-label design, strong inferences cannot be made about the treatment's therapeutic efficacy. However, the data do suggest that further research is warranted. The response rate to psilocybin was 67% (n=8) at 1 week after treatment (HAM-D and BDI), and seven of these eight patients also met criteria for remission. Moreover, 58% (n=7) of the patients maintained their response for 3 months, and 42% (n=5) remained in remission. It is also worth noting that psilocybin has a favourable toxicity profile and is not associated with compulsive drug-seeking behaviours in animals or human beings. The side-effects that we noted were minor, and expected in light of previous studies of psilocybin. (Carhart-Harris et al., 2016, p. 626)

Research with psilocybin extends beyond just the realm of affect disorders. In fact, the pharmacological action may not only be useful for affect disorders such as depression, but useful in the treatment of addiction.

Psilocybin and Addiction

Dr. Matthew Johnson et al. (2014) in the Journal of Psychopharmacology, investigated the possible role psilocybin could play with the treatment of tobacco addiction. Tobacco addiction is a public health crisis, similar to other disorders, that takes a toll on the health of the individual consuming tobacco products. Studies within the past decade have shown that psychedelics like LSD have a positive effect on the treatment of alcoholism (Krebs & Johansen 2012). This begs the question, what other addictions can be treated with psychedelics, and are all addictions created equal? It goes without saying, that different addictive substances have varying effects both psychologically and physiologically. As far as what psychedelics might be promising for halting various addictions, it's not quite clear.

Despite the lack of scientific consensus regarding the efficacy of various psychedelics for different addictions, it is clear that serotonergic modulation is key. It is known that the 5-HT_{2A} receptor plays some role in the release of dopamine release in the nucleus accumbens and striatum (Porras et al., 2002). As previously stated, psilocybin binds to the 5-HT_{2A} receptor; this to say that it could potentially disrupt dopaminergic activity associated with addiction.

In addition to the biological binding profile, psilocybin is promising to researchers due to its ability to produce mystical experiences. This has been hypothesized to generate deep introspection which may lead to the increase in desire to quit substance abuse (Johnson et al. 2014). The study by Johnson et al. investigated psilocybin with this understanding in mind. In this pilot study, fifteen individuals were enlisted in a fifteen week course of cessation treatment including psilocybin administration. Cognitive Behavioral Therapy was used in preparation for these treatments to motivate quitting the day of the psilocybin session. Therapy was also available to participants during the psilocybin session to assist with any experience related concerns. Blood pressure and heart rate were monitored through the psilocybin session to measure the safety of the substance in the clinical setting.

During this study, a course of psychological tests was administered including various questionnaires regarding mysticism, cigarette dependence and state of consciousness. These were used to quantify the subjective effects of psilocybin and how they affected participant's dependence to tobacco. Participants also had to prove that smoking cessation had occurred by measured CO exhalation and urine tests. When the researchers followed up with their patients at the six-month mark, 80% had remained abstinent from cigarettes. This study is one of the few that has been published regarding psychedelics as a treatment for addiction, but the results call for more research to be conducted.

With preliminary success, more research needs to occur in order to further understand the biological mechanisms. In addition to the biological mechanisms, psychological evaluation is an integral part of the research. Similar to the previous studies mentioned, the sample size is quite small which means that results are not as conclusive as they seem despite the statistical analysis. The next step forward in the scientific community's understanding of these substances should include larger sample sizes. Other areas of interest may include different ways of determining neurological mechanisms through MRI or blood tests. This may yield further insight into the underlying mechanisms beyond psychological parameters.

Neuroimaging with Psilocybin and LSD

Two studies by Dr. Carhart-Harris et al. published in the Proceedings of the National Academy of Sciences (PNAS) conducted neuroimaging of participants under the influence of psilocybin (2012) and LSD (2016). The first study with psilocybin used Blood Oxygen Level Dependent (BOLD) signal from functional MRI to better understand brain connectivity under the influence of psilocybin. The study of varying blood flow and interconnection between brain regions is an important aspect to understanding psychedelic's neurobiological effects. Carhart-Harris et al. reported that psilocybin caused a, "significant decrease in positive coupling between the medial Prefrontal Cortex and the Posterior Cingulate Cortex" (2012). They go on to claim that this implies that the perceptual/conscious changes are brought about by the decreased activity and connectivity between these two regions. This result is critical, as these regions are heavily implicated in the theory of the Default Mode Network, which will be discussed in detail in the next section.

In the 2015 study, a similar approach was taken with LSD. LSD is very similar in action to psilocybin, but varies in the sense that it is an ergot-derived substance that is synthesized in the lab, rather than being found in natural sources. LSD had similar effects on BOLD signal as did psilocybin. This study took a more direct approach to understanding the meaning of ego-dissolution and loss of sense of self. These patients showed decreases in connectivity between the parahippocampus and the retrosplenial cortex (2015). According to Dr. Carhart-Harris et al., these results imply that one's sense of self is partially or wholly maintained by the connectivity and functionality of this particular brain network (2015). The authors also make the assertion that, "More broadly, the results reinforce the view that resting state ASL, BOLD FC, and MEG measures can be used to inform on the neural correlates of the psychedelic state," which has huge implications as far as understanding various states of consciousness and their neural correlates (Carhart-Harris et al. 2015). This research seems to be heading in the direction of clinical application to these psychiatric illnesses, but much needs to be understood about the metacognitive processes at play while under the effects of these substances.

"Brain Entropy" and the Default Mode Network

An interesting theory brought forth on the psychological/neurobiological effects of these substances is The Theory of the Entropic Brain. The neurobiological mechanisms are important for describing what is going on within organism, but one has to beg the question of the psychological and conscious activities that psychedelics bring about. In The Theory of the Entropic Brain, the complexities of states of consciousness are described by Dr. Robin Carhart-Harris et al. (2014). He postulates that systems entropy applied to the brain could explain behavioral and conscious disturbances after a certain stimulus is applied to the system, such as a psychedelic drug. According to Carhart-Harris, using psychoanalytical references and an understanding of systems entropy, a construction of the psychedelic conscious state can be made.

Psychedelics are understood, based upon the fMRI studies previously done, to disorganize brain activity. In cognitive neuroscience, higher level brain activity needs to be organized to form something known as the Default Mode Network (DMN). It is postulated that the DMN is separate from basic sensory networks, and is used primarily during higher-functions such as self-reflection, and other metacognitive operations (Carhart-Harris et al. 2014). It is important to note that the brain region associated with the DMN has a metabolic rate 40% higher than that of the average of rest of the brain (Carhart-Harris et al., 2014). The DMN is key when discussing psychedelics, because a hallmark of the psychedelic experience is self-reflection and self-realization.

Psychedelics are considered a pharmacological option for disrupting the DMN. If the postulation that the DMN controls high-functions in the brain, psychedelics inherently disrupt the higher functions like self-realization. This goes hand in hand with claims that psychedelics dissolve ego or self (Carhart-Harris & Nutt, 2010). When talking about the therapeutic potential for psychedelics, it is important to keep this aspect of the drugs in mind. Psychedelics in essence can dissolve the boundaries between one's self and the environment or elements of the environment around them. This supports the claim of MDMA being able to open PTSD patients up to talk with their therapist. The limitations of this idea have yet to be defined, but wide-reaching implications can be surmised. It was reported, that a single high dose of psilocybin induced an existential experience in participants of one study that had a lasting beneficial effect on the subject's well-being (Griffiths et al. 2006).

A key aspect in understanding the mechanisms of treatment, whether it be addiction, anxiety, or affect disorders, is the ability to discern neurological changes from psychological tests. With an increasing amount of research being done with these substances over the past decade, a better understanding of therapeutic application is being obtained. By expanding the understanding of psychedelic's modulation of neurobiological mechanisms and psychological well-being, a more decisive approach can be taken when applying these drugs to various psychiatric uses. A consensus has been reached regarding the specific binding of most of these psychedelic drugs (Green et al., 2003, Franz et al., 1997, Passie et al., 2008), but the wide-ranging effects that these drugs have on the nervous system and mind are yet to be completely mapped.

In addition to the neurobiological mechanisms of psychedelics, the psychological weight that these drugs carry must also be taken into consideration. These substances have the potential to elicit mystical experiences (Griffiths et al., 2006). Despite the somewhat colloquial term, these experiences can be quite troubling for the individual who undergoes treatment with these substances if they do so without proper guidance. That is why it is imperative that these substances remain within the realm of clinical treatment with therapy available to individuals who undergo this treatment. Mithoefer et al. stated in their study with MDMA.

> If MDMA-assisted psychotherapy is ultimately approved for use in clinical practice, it would likely occur in clinics specifically equipped for longer treatment sessions and overnight stays. This method also involves patient preparation and close follow-up to support further processing of emotions and integration of cognitive shifts that may occur. Both the preparation sessions and the integration sessions appear to be important for safety and therapeutic effect. (2010, p. 12).

This statement can be applied to the entire spectrum of future psychedelic treatment, and should not only represent concerns with MDMA, but the myriad of other substances as well.

Conclusion

Research of psychedelic drugs is on the rise as more institutions publish promising preliminary results. While reading into these studies, it is important to understand the scope of the published results. One of the biggest hindrances to these studies is the small sample sizes that are available to researchers. Developing psychiatric treatment takes a significant amount of time, not only to determine its efficacy, but also the safety profile. Psychedelic research needs to undergo the same rigorous scientific scrutiny that other treatment options do. In order to do this, the stigma surrounding these substances needs to be addressed. Currently it is difficult for researchers to submit a grant hoping to identify clinical applications for these drugs, as the vast majority of research with these substances has been to elucidate harmful or negative properties. Most of the funding for this research (in the United States) comes from either the National Institute of Health, or the National Institute of Drug Abuse, and their priorities have been centered around understanding the potential public health risks these drugs pose. This a one-sided approach in many ways. What has been found is that the scheduling of these substances prohibits or severely stagnates the research of their effects and potential therapeutic utility. For psychedelic treatment options to gain enough legitimacy in order to be considered for FDA approval, larger sample sizes, side-effect/safety profiles, and target illnesses need to be established. Beyond this, psychedelics are unlike any other drug commonly seen in research, as they carry the ability to dissolve an individual's sense of self, and to a degree that seems beneficial in the long term. To what degree and to what cost are all topics that can be further illuminated by continued research. More research needs to be conducted in the coming years to fully understand the potential that these substances have in psychiatry.

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