Psychedelics as a Tool for Therapy

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Let’s start at the beginning, despite modern biases, psychedelics have been consumed by humans since before humans were humans. It is likely that ancient Hominins consumed psychedelic mushrooms off the forest floor (Arce & Winkelman, 2021). The first studies on psychedelics as a tool for the brain started in the 1950s, about 12 years after Albert Hofmann synthesized LSD for the very first time in human history and about 7 years after Hofmann became the first in human history to ingest it (Doblin Et Al. 2019). In 1971 Nixon enacted the Controlled Substances Act which banned the use of psychedelics. This almost singlehandedly put a pause on psychedelic research for the next three almost four decades. Today we are in a new renaissance of psychedelic research with more ongoing studies than ever before, including: MDMA or Ketamine for PTSD, Psilocybin for existential anxiety about terminal illness or imminent death, and Ketamine for depression. Over the course of this paper, we will analyze the efficacy and safety of psychedelics as neurotherapeutics. I will explain what we know about how psychedelics interact with the mechanisms of the brain and how it is beneficial for mental health aide, a bit of the history of studies on the topic and what some recent studies are finding, and whether the psychedelic effects of psychedelics are really necessary at all.

**The neuroscience**

The human brain is one of the most, if not the most, complicated machines on the planet. The human brain consists of on average 86 billion neurons (Carhart-Harris, 2019), these neurons connect to form intricate patterns that send and store information and stimuli throughout the brain. These patterns form pathways that form networks, and it all happens in a very complex and precise way with the outcome being the human brain and the emergent property we call consciousness. The neurons in your brain come with a bunch of different kinds of receptors that release and connect to different amino acids or neuropeptides called neurotransmitters. Some of the neurotransmitters in your brain include dopamine, glutamate, serotonin, and GABA. (Gibb, 2015) Your brain has receptors all throughout with the intent of binding with some of these neurotransmitters. An example of this would be the 5-HT2A receptors, these ones want to bind with the serotonin in your brain. Sometimes a chemical or substance called an agonist, it is a substance that can bind to a receptor and cause it to activate in the same biological way as it normally would. That is precisely how serotonergic psychedelics work, they bind to our serotonin and dopamine receptors and cause them to fire. Lysergic acid diethylamide (LSD) is one such psychedelic, it binds to the 5-HT2A serotonin receptors in the brain and induces a higher level of neuroplasticity. Compared to other psychedelics that fall under the same category such as psilocybin, LSD lasts a much longer time, this is because its unique shape gets stuck onto your receptors (Clarke, 2017). During this agonism of the 5-HT2A receptors also causes an asynchronous mode of glutamate release, glutamate being a neurotransmitter that excites other neurons and causes them to fire more. The brain gets disrupted in a way that causes a desegregation between different brain networks (Carhart-Harris, 2019). The brain being in a state of higher neuroplasticity and higher activity across the board causes a relaxation of prior beliefs and expectations (Ibid.). With the assistance and guidance of a trained therapist this state can be utilized to treat a variety of our most common and harshest mental illnesses including PTSD, depression, existential anxiety about terminal illness or imminent death, and addiction. Let’s take a look at some of these aforementioned studies. An MDMA-assisted therapy trial on people with severe PTSD, a Ketamine Assisted Psychotherapy study on those suffering from treatment resistant depression.

**The Studies**

In a study published in 2021 researchers ran a randomized, double-blind, placebo-controlled study where they administered MDMA or placebo to patients while treating them for PTSD. After screening preparations are complete the patients go through 3 experimental treatments. At the experimental session they are given either MDMA or a placebo and treatment, following the experimental session they receive 3 integration sessions and an assessment. Treatment efficacy on patients was measured via the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and the Sheehan Disability Scale. The first scale used to diagnose and assess short- and long-term PTSD symptoms, the latter measuring how functional impaired the subject is in work/school, social, and home lives. The study found “with manualized therapy over the course of 18 weeks results in a significant and robust attenuation of PTSD symptoms” (Mitchell, 2021). All participants CAPS-5 scores went down, but the MDMA participant pool had their average score decline by 24.4 points compared to the 13.9 average decline of the placebo participants. During the duration of the study safety was also closely monitored. During the study there were some Treatment-emergent adverse events (TEAEs), the TEAEs of the MDMA pool of participants were largely minor and temporary problems such as muscle aches and elevated temperature. The TEAEs of the placebo pool of participants on the other hand were significantly more severe, two participants reported a serious adverse event in which they had experienced suicidal ideations, one participant of which needed hospitalization. This study found that PTSD treatment with MDMA paired with manual therapy is a more effective and safer than manual therapy on its own, the next step is to run a study comparing this method with the use of selective serotonin reuptake inhibitors, one of the currently more adopted and effective treatments we use.

In a study published in 2019 researchers, led by Jennifer Dore, assess the efficacy of Ketamine Assisted Psychotherapy (KAP) to help with a variety of conditions, such as major depressive disorder, developmental trauma, ADHD, PTSD, Generalized Anxiety Disorder, obsessive compulsive disorder, and miscellaneous mood, anxiety and substance use disorders. Coming in to the study all 235 patients had to fill out baseline assessments including the Beck Depression Inventory (BDI), Hamilton Anxiety Scale (HAM-A), Patient Health Questionnaire , Childhood Resilience Scale, and the Adverse Childhood Scale. The patient then receives a KAP session with under the tongue (sublingual) administration. The administration amount here should be fairly low, the goal being to get the patient into a dissociated yet conscious and communicable state for therapy titled the “Trance State”. After the session the patient then completes another round of assessments, specifically the change of state, mystical experience questionnaire (MEQ), and the ego dissolution index, while the therapist records their observations of the patients experiences. With this information the take-home prescription is calculated and the patient is instructed to take the ketamine sublingually up to but not exceeding six sessions in a two week period. Generally, two weeks later the next in-office KAP session will occur, this time with intramuscular administration, the goal being to get the patient to a state labeled the “Transformational State”, in this state the patient loses most body and sensory awareness and is more likely to experience a mystical or out of body experience. The study found that the treatment lowered depression and anxiety according to the BDI and HAM-A scales, and that the treatment was more effective on those with higher baseline scores (Dore, 2019). “Significant regulatory hurdles and issues related to abuse potential will need to be overcome if patients are to benefit from [such] dosing regimen” (Olson, 2020). Despite the patients being granted a prescription for this trial, at-home psychedelic use still has a long way to go.

**How necessary are the subjective effects?**

So far it looks like psychedelics always have been, currently are, and will be an effective tool for therapy, but what about the effects that draw the attention of those who trip recreationally? Do we need the more subjective effects in order to gain the therapeutic benefits? This is the question that some, specifically David E. Olson, have been asking, and for good reason. The subjective effects are the primary attractor for recreational use and abuse of psychedelics, and recreational use was a contributing factor to the drugs being banned in the Controlled Substances Act. This in turn negatively affected public opinion and interest on psychedelics and their research and likely cost years of time in research and studies. In his paper Olson states, “Despite the promising therapeutic responses produced by psychedelic-assisted therapy, the intense subjective effects of these drugs make it unlikely that they will ever become widespread treatments for disorders such as depression” (2021). If we can separate the subjective effects from the gained neuroplasticity and therapeutic gains, then we could have a very safe and effective treatment for some of our worst and most common mental illnesses. In a 2020 study on rats, researchers found that a derived analog to ibogaine, a psychedelic that hails from Central African iboga trees, called tabernanthalog has all of the psychoplastogenic benefits seemingly without the hallucinatory subjective effects or other unwanted side effects. Ibogaine, the naturally occurring psychedelic component in iboga fruit, is considerably unsafe, it is somewhat cardiotoxic, hallucinogenic. “However, several safety concerns have hindered the clinical development of ibogaine, including its toxicity, hallucinogenic potential and tendency to induce cardiac arrhythmias” (Cameron, 2020) This is the problem that the researchers wanted to solve, and if the effects of tabernanthalog on humans are like that of rats then they quite possibly have.

Despite these findings many researchers believe quite the contrary, that the subjective effects are a necessary component of the therapeutic effects. Agonism of the 5-HT2A receptors causes the heightened neuroplasticity that we seek, and the subjective effects. When the 5-HT2A receptors are purposefully blocked before ingestion, the subjective effects and neuroplasticity are no longer observed. It is currently unknown if the 5-HT2A receptors cause both phenomena, and if the phenomenon can be separated. Separation is not the goal, “Scores on questionnaires assessing mystical-type experiences are predictive of beneficial outcomes from psychedelics administered in experimental contexts” (Yaden, 2020). The data shows that there is a correlation between a larger change in condition with larger scores on the MEQ. It is important to note that the correlation in change is specifically with the intensity of the mystical experience, and not the intensity of the psychedelic experience overall. “Studies have repeatedly shown that participants frequently rate their psychedelic experiences as among the most meaningful of their entire lives and they are sometimes compared to the birth of a first-born child or death of a parent” (Ibid.). Experiences like this help cement the positive therapeutic effects as permanent or long-term in nature.

**Conclusion**

Psychedelics may be considered party drugs by many, but when you stop to take a look, it seems that there is more than meets the eye when it comes to psychedelics in therapy. Hopefully they can be better known as the next groundbreaking solution to mental health. The FDA has approved MDMA and psilocybin for phase 3 testing. The objective of phase 1 testing is to prove safety of a treatment, phase 2 proves that the treatment is effective, and phase 3 proves that the treatment is as good as or better than the current methods. This means that psychedelic therapy may be closer than you think. With psychedelics being unanimously understood as an invaluable tool in the therapy world, and the FDA designating psychedelic therapy a breakthrough technology, it will only be a matter of time until psychedelic therapy is out there making a difference.

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