

EDITORIAL

Novel psychotherapeutics – a cautiously optimistic focus on Hallucinogens

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1. A renewed interest in hallucinogens

Disrupted mental health affects up to one in three individuals globally and is an unmet medical challenge contributing to individual suffering as well as significant societal and economic burden [1]. In response to the stalled development of new drugs and a greater than ever need for novel therapies to treat psychiatric illness, the last two decades have seen renewed scientific and medical receptiveness to the idea of treating several mental disorders with drugs commonly known as hallucinogens.

'Hallucinogens,' in a general sense, define a vast and diverse set of molecules that elicit significant alteration in human consciousness by acting on targets in the central nervous system, temporarily rerouting synaptic transmission in the brain. Commonly accepted classes of hallucinogens include psychedelics, entactogens, dissociatives, and atypical hallucinogens that include deliriants, cannabinoids, and kappa opioids. Each class possesses its own unique attributes and subclasses as well as some degree of overlap with regard to perceived effects, pharmacology, and/or potential therapeutic utility [2].

The therapeutic use of hallucinogens represents a potentially new paradigm in the way medicine understands and treats psychiatric illnesses. While the pharmacological diversity of hallucinogens is vast, a fascinating common phenomenon has been observed in their therapeutic utility: a single acute exposure to the hallucinogenic agent can elicit an immediate and lasting improvement in symptoms for the patient, an effect that persists long after the drug is metabolized and gone from the body [3]. This is in contrast to current pharmacotherapies used to treat mental disorders, such as selective serotonin reuptake inhibitors (SSRIs), which are based on a therapeutic model that attempts to alleviate symptoms by re-equilibrating the steady-state levels of serotonin in the brain using a chronic dosing regimen of the drug.

The evolution of novel therapies to treat psychiatric conditions is inevitable as new tools and technologies contribute to our understanding of the intricate mechanics of the brain [4]. Unquestionably, the hallucinogen's unique ability to perturb consciousness provides a compelling tool to help understand the connectivity of the brain in relation to the genesis of self-awareness and introspection. While the molecular pharmacology of most hallucinogens has been established, the complementary biological mechanisms responsible for their observed

effects on the psyche are only beginning to be understood [5]. As more rigorous scientific data emerges from clinical research, combined with the availability of modern brain-imaging techniques, we are provided with newly generated insight into the mind [6]. This insight will provide a foundation and rationale for the way that we understand the brain, ultimately leading to the development of novel approaches to treating mental illness.

2. Public perception and regulatory troubles

A contemporaneous paradigm shift occurring alongside the renewed scientific and medical interest in hallucinogens is a change in perception by the public and by regulatory agencies. These changes include the approval of several Phase 3 clinical trials by the US FDA, a variety of recent positive reports in mainstream news outlets, and the US Drug Enforcement Administration (DEA)'s willingness to work with researchers and clinicians to grant the appropriate legal authorizations to handle otherwise illegal compounds. All are examples of perceptions shifting away from the fears originally brought about by the association of hallucinogens with the complex cultural changes that occurred in the 1960s and 1970s.

The cooperation of the law-enforcing entities such as the DEA is especially critical. Most of the hallucinogens being tested in the current FDA-approved clinical trials fall into the DEA's Schedule I classification, which attempts to label drugs with high potential for abuse and having *no medicinal value*. Therein lies a significant challenge. How does a researcher study the medical utility of a drug that has been labeled medically useless and illegal? Once a compound has been declared Schedule I, it becomes increasingly onerous to obtain and handle legally, and researchers are often either unwilling or afraid to take the necessary steps to achieve access.

The scheduling rationale behind hallucinogens is especially challenging to comprehend in light of the less-restrictive classification of many other psychoactive drugs with medical utility and high abuse potential such as amphetamine. Given the emerging data demonstrating the medical safety and efficacy of several hallucinogens (outlined later), the support of federal regulatory and funding agencies will be imperative in increasing research into these potentially valuable medicines.

3. Psilocybin, LSD, and terminal illness diagnosis distress

Psychedelics represent one of the more studied classes of hallucinogens in terms of pharmacology and potential clinical utility [7]. The effects produced by psychedelic drugs are principally mediated through the serotonergic 5-HT_{1A/2A} receptors, which are found widely in the central and peripheral nervous system, including the cerebral cortex, hippocampus, amygdala, and raphe nucleus, and have been shown to modulate attention, working memory, and cognition/perception. The common effects reported by users of psychedelics include alterations of sensory perception, ego loss, and increased awareness of the present leading to sometimes-profound personal insight and even mystical experiences [8]. The individual's state of mind and the set and the setting of the experience have been hypothesized to largely influence the magnitude of each aspect of the psychedelic drug's effects, and guides with specialized training are typically present to facilitate the experience in a clinical setting.

Upon its serendipitous discovery in 1943 by the Swiss chemist Albert Hoffman, lysergic acid diethylamide (LSD) became the prototypical psychedelic compound for clinical study in the 1950s until the Controlled Substances Act brought a halt to research in 1970. Though the majority of contemporary psychedelic studies have avoided LSD due to its controversial reputation and relatively long duration of action, several recent small clinical studies have been conducted in Switzerland and the UK [9]. In particular, one double-blinded placebo-controlled pilot study aimed to understand the safety and efficacy of LSD for treating the anxiety associated with terminal illness diagnosis; the observed trends were promising and support further study in larger trials [10].

With relatively similar effects to LSD and a shorter duration of action, the natural product psilocybin, a fungal tryptamine and also first characterized by Hoffman, has recently been the focus of two expanded clinical trials aimed at addressing depression and anxiety in terminally ill cancer patients. The trials were designed around a coupled experience with the drug and psychiatric guidance. Phase 2 trials at Johns Hopkins University and New York University have been conducted under rigorous double-blinded placebo-controlled conditions [8,11]. In both studies, a majority of patients demonstrated both immediate improvements in self-reported measures of anxiety and depression and 60–80% of patients exhibited clinically significant sustained decreases in depression and anxiety at 6-month follow-up visits. The outcomes have been described as 'unprecedented' in psychiatry [12]. Follow-up multi-site Phase 3 clinical trials are currently being planned by the non-profit Heffter and Usona Research Institutes.

4. MDMA and severe post-traumatic stress disorder

In the mid-1970s, the experimental psychopharmacologist Alexander Shulgin first suggested the therapeutic potential of the prototypical entactogen, 3,4-methylenedioxymethamphetamine (MDMA) [13]. Entactogens are characterized by their ability to induce openness and connection with others, and MDMA saw early esoteric clinical use as a tool in couples

therapy. However, the increasing casual abuse of MDMA overshadowed its therapeutic potential in the eyes of lawmakers and by the late 1980s MDMA was illegal in most countries. Despite its recreational reputation and some concerns about safety, mounting data has supported the clinical use of MDMA again, specifically as a psychotherapeutic tool for patients with severe post-traumatic stress disorder; in a single therapeutic session, it has been shown that MDMA can grant patients the ability to access and confront difficult traumatic memories, which has been hypothesized as a factor contributing to the success of the trials [14]. In response to the positive outcomes in Phase 2 clinical trials with MDMA for severe post-traumatic stress, the FDA has subsequently granted Breakthrough Therapy Designation to the non-profit Multidisciplinary Association for Psychedelic Studies to advance further studies. Preparation for Phase 3 trials is currently underway; these landmark trials represent, for first time, hallucinogen-assisted psychotherapy being evaluated for possible prescription use.

5. Ketamine's unique antidepressant effect

Dissociatives are generally characterized by their ability to distort the user's perception of sight and sound and to elicit illusions of detachment from the environment or one's self. Ketamine is a dissociative anesthetic that was first synthesized in 1962 while in search of an anesthetic alternative to phencyclidine (PCP) that was devoid of PCP's tendency to cause hallucinations and occasionally violent behavior. Ketamine likely achieves a dissociative effect by antagonizing the N-methyl-D-aspartate receptor in addition to polypharmacology at other receptors in the central nervous system (CNS). Ketamine has been of particular interest in light of numerous controlled studies describing the compound's rapid and relatively sustained (4–10 days) antidepressant effect [15]. While the aforementioned hallucinogens tend to involve an element of guidance, introspection, and self-discovery associated with their positive clinical outcomes, ketamine may work through a less subjective, more biochemically driven 'reset' type of mechanism [16]. Nevertheless, ketamine's precise short-term and long-term neurobiological effects are still not well understood and a possible pharmacological convergence with the therapeutic effects of psychedelics cannot be ruled out. Insight into ketamine's mode of action will likely provide models by which to develop new antidepressants [17]. Once again, however, ketamine's use as an antidepressant has been controversial, as it is also a Schedule III controlled substance due to its occasional recreational use.

6. Concluding remarks

The clinical and scientific consensus toward hallucinogens as novel psychotherapeutic agents has been generally optimistic; however, caution and due diligence must be observed if continued research is to occur. As the pendulum again swings in favor of studying and utilizing hallucinogens with the ultimate goal of benefiting society, a challenge to consider will be ensuring the absence of scientific and interpretive bias, especially given the recreational appeal of many of these

substances. We must also be careful toward zealously viewing powerful psychoactive drugs as ‘silver bullets.’ The future success of hallucinogen-based therapies will depend first on the application of ethically sound and rigorous scientific methods toward the continued demonstration of significant clinical outcomes combined with rethinking how we perceive and regulate these compounds. While potential for the misuse of hallucinogens cannot be discounted, we must ultimately ask ourselves: could their medical benefit potentially outweigh the harm in facilitating the availability of these compounds to clinicians and researchers? If armed with irrefutable evidence of efficacy and safety, it will be up to motivated scientists and medical professionals to become politically vocal in seeking the necessary changes.

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