U.S. FOOD & DRUG ADMINISTRATION

National Institutes of Health

JUN 13 2019

The Honorable Brian Schatz
United States Senate
Washington, DC 20510-1105

Dear Senator Schatz:

Thank you for your inquiry to the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) regarding research on the use of psychedelic drugs to treat mental illnesses. NIH supports a robust portfolio of basic and clinical research for therapeutic discovery and development. Please find responses to your individual questions below.

1. **Please provide your research agenda for investigating the use of psychedelic drugs, including LSD, ketamine, MDMA, psilocybin, and ibogaine to treat mental health illnesses.**

Over the last 10 years, the number of projects funded by the National Institute of Mental Health (NIMH) investigating the use of psychedelic drugs to treat mental illnesses has increased (with the largest increase occurring from 2009-2013; project numbers have been somewhat stable since then). This appears mainly due to an increase in projects exploring the use of ketamine for patients with acute suicide risk and/or treatment-resistant depression. In addition, research on other psychedelic drugs holds promise for uncovering mechanisms of illness and possible interventions, ultimately leading to novel treatments with fewer side effects and lower abuse potential. Some examples of NIMH-funded research on psychedelic drugs follows.

Ketamine, an anesthetic approved by FDA in 1970, is emerging as a potential rapid-onset intervention for acute suicide risk and treatment-resistant depression. Ketamine is associated with rapid – within minutes to hours – decreases in depression and suicidal thoughts. Although these effects are transient – lasting approximately 1 week with a single administration – the findings are promising and have been replicated in several studies.[1,2] NIMH, through both intramural and extramural research programs, is funding ketamine research to determine the correct dosages, potential mechanisms of action, potential related compounds, and which individuals might best respond to ketamine. For example, NIMH scientists and collaborators found that ketamine's antidepressant effects may be due to a metabolite – a byproduct of ketamine's chemical breakdown – and not ketamine itself.[3] Their research also suggests that the ketamine metabolite may produce beneficial effects without inducing hallucinations or abuse

[1] https://www.ncbi.nlm.nih.gov/pubmed/20673547
[2] https://www.ncbi.nlm.nih.gov/pubmed/28969441
[3] https://www.ncbi.nlm.nih.gov/pubmed/27144355

potential. In March 2019, FDA approved Spravato, an esketamine nasal spray that should be taken in conjunction with an oral antidepressant, for treatment-resistant depression in adults.[4,5] This treatment is only available at a certified doctor's office or clinic to mitigate potential risks. The makers of Spravato are also conducting clinical trials of intranasal esketamine in participants at imminent risk for suicide.[6,7]

As another example, NIMH is funding basic research to elucidate the underlying mechanisms of psychoactive drugs, such as lysergic acid diethylamide (LSD). One such study is using high-tech snapshots achieved through x-ray crystallography to examine how drugs bind to and modulate the activity of their receptor sites of action.[8] In 2017, NIMH-funded researchers unveiled the molecular structure of LSD interacting with its receptor in the human brain.[9,10] The findings provide the first structure-informed insights into the molecular mechanisms of a hallucinogen. In addition, these findings may hold clues to the roots of psychopathology and consciousness and may accelerate the discovery of new treatments for serious mental illnesses such as schizophrenia and depression.

Researchers are also interested in the therapeutic potential of 3,4-methylenedioxy-methamphetamine (MDMA; also known as Ecstasy), a synthetic drug that alters mood and perception. MDMA is currently in clinical trials as a possible treatment aid for post-traumatic stress disorder and anxiety in terminally ill patients, and for social anxiety in autistic adults.[11,12] NIMH-funded researchers are using behavioral pharmacology, brain region-specific drug injection, optogenetics, and imaging of neuronal activity during behavior to identify the neural circuitry and synaptic physiology that produce MDMA's prosocial effect.[13] This basic research could pave the way to the development of compounds with improved safety or efficacy profiles and reduced abuse liability.

The National Institute on Drug Abuse (NIDA) has previously funded research on ibogaine (a hallucinogenic West African shrub) and structurally related compounds as a potential therapy for opioid addiction. However, while there were early signs of effectiveness, this research also uncovered safety concerns. Studies found that ibogaine could be toxic to nerve cells in the brain (particularly in the cerebellum), and there are reports of ibogaine-related deaths that suggest it is toxic to the muscles of the heart, causing arrhythmia and, in some cases, cardiac arrest. Given that these potentially fatal complications outweighed the potential benefits, ibogaine was determined not to have therapeutic potential.

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[4] Ketamine is a chemical mixture of esketamine and arketamine.
[5] https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified
[6] https://clinicaltrials.gov/ct2/show/NCT02133001
[7] https://www.ncbi.nlm.nih.gov/pubmed/29656663
[8] https://projectreporter.nih.gov/project_info_description.cfm?aid=9447206
[9] https://www.ncbi.nlm.nih.gov/pubmed/28129538
[10] https://www.nimh.nih.gov/news/science-news/2017/revealed-lsd-docked-in-its-human-brain-target.shtml
[11] https://www.drugabuse.gov/publications/drugfacts/mdma-ecstasy-molly
[12] www.ClinicalTrials.gov
[13] https://projectreporter.nih.gov/project_info_description.cfm?aid=9468429

2. What gaps exist in our understanding of the medical potential for these psychedelic drugs?

Further research is needed to examine the efficacy and long-term safety of psychedelic drugs, including with repeated exposure and potential interactions with existing treatments. It is also important to understand their mechanisms of action in order to identify new targets that preserve the therapeutic effect and minimize negative side effects.

NIMH encourages research on the development and testing of pharmacological interventions (including, but not limited to, use of psychedelic drugs) through a dedicated set of Funding Opportunity Announcements (FOAs). These FOAs include a cooperative agreement mechanism (U01) and phased research project grant mechanism (R61-R33) that provide support for early intervention development and testing (e.g., for studies that test novel pharmacological agents, for studies that propose the use of existing drugs or 'repurposing' for novel mental-health-relevant targets). Additional FOAs provide support for testing the effectiveness of drugs with previously established efficacy (alone or in combination with other drugs or non-pharmacological alternatives), in community practice settings. Furthermore, NIMH requires an experimental therapeutic approach for the development and testing of therapeutic interventions, in which the studies not only evaluate the clinical effect of the intervention but also generate information about the mechanisms underlying a disorder or an intervention response.

3. What has the FDA and NIH found in terms of safety and potential for abuse for the drugs?

Of the drugs discussed above, only ketamine, including the enantiomerically pure stereoisomer esketamine in FDA-approved Spravato, is controlled outside of Schedule I of the Controlled Substances Act (CSA). Ketamine, approved for use as an anesthetic, and esketamine, approved for treatment-resistant depression, are controlled in Schedule III as drugs with currently accepted medical uses in the United States and a degree of abuse potential and dependence liability appropriate for control in Schedule III. Other psychedelic drugs, such as LSD, MDMA, and psilocybin, are controlled in Schedule I because they have a high potential for abuse and no currently accepted medical use in the United States. A drug must have a currently accepted medical use in the United States for the drug to be placed in Schedules II, III, IV, or V through the administrative drug scheduling process (21 U.S.C. 811 (b-c)).

NIDA supports a robust portfolio of basic and clinical research on drug use, its consequences, and the underlying mechanisms. Additional research is needed to evaluate the risks associated with psychedelic drugs and their potential use to treat mental illnesses, particularly the effects of long-term use on health and behavior, and their potential for misuse. It is important to note that a dose that is safe and efficacious for therapeutic purposes may be different from a dose used for recreational purposes. For example, the FDA-approved treatment Spravato (esketamine, described above) must only be administered in a medically supervised, certified healthcare setting and not dispensed to patients outside the healthcare setting. This helps ensure the dose can be limited to the amount that is efficacious for therapeutic purposes. Hence, the risks associated with therapeutic use are not necessarily the same risks an individual would face when taking these drugs recreationally.

Ketamine

Ketamine is a dissociative anesthetic, so called because it distorts perceptions of sight and sound and produces feelings of detachment from the environment and self.[14] At moderate to high doses, ketamine can cause sedation, immobility, and amnesia. At high doses, ketamine users report experiencing terrifying feelings of almost complete sensory detachment likened to a near-death experience. Use of dissociative drugs can also cause anxiety, memory loss, and impaired motor function, including body tremors and numbness. These effects, which depend on the amount of the drug taken, are also unpredictable – typically beginning within minutes of ingestion and lasting for several hours, although some users report feeling the drug's effects for days. There are also risks to long-term ketamine use: long-term ketamine users may develop conditions that include ulcers in the bladder, kidney problems, and poor memory.

There is evidence that ketamine has the potential to be addictive, resulting in the drug being placed in Schedule III of the CSA.[15] There have been reports of people binging on ketamine, a behavior that is similar to what is seen in some cocaine- or amphetamine-dependent individuals, and ketamine users can develop signs of tolerance and cravings for the drug. Researchers have found that ketamine can be safely administered at low doses and that the side effects are short-term.

LSD and Psilocybin

In the short-term, LSD and psilocybin can cause profound distortions in a person's perceptions of reality.[16] Their effects can begin within 20 to 90 minutes and can last as long as 6 to 12 hours, with the most common effect being hallucinations, which can be unpleasant or negative. Other short-term effects include increased heart rate, nausea, intensified feelings and sensory experiences, and changes in the perception of time. Some users also experience increased blood pressure, breathing rate, or body temperature, loss of appetite, dry mouth, sleep problems, synesthesia (i.e., mixed senses such as "seeing" sounds or "hearing" colors), feelings of relaxation or detachment from self/environment, uncoordinated movements, excessive sweating, panic, paranoia, or psychosis.

Little is known about the long-term effects of such hallucinogens. Overall, two long-term effects – persistent psychosis and flashbacks to hallucinated experiences (called hallucinogen persisting perception disorder, or HPPD) – have been associated with use of LSD and psilocybin. Although the occurrence of either is rare, it is also unpredictable and may happen more often than previously thought, and sometimes both conditions occur together. While the exact causes are not known, both conditions are more often seen in individuals with a history of psychological problems, but these issues can happen to anyone, even after a single exposure. There is no established treatment for HPPD, in which flashbacks may occur spontaneously and repeatedly (although less intensely than their initial occurrence). This is another area where more research is needed to accumulate sufficient evidence.

Research suggests that LSD and psilocybin do not cause compulsive and uncontrollable drug-seeking nor does their discontinuation typically cause withdrawal – effects that are viewed as

[14] https://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts#ketamine
[15] https://www.deadiversion.usdoj.gov/schedules/index.html
[16] https://www.drugabuse.gov/drugs-abuse/hallucinogens

hallmarks of addiction and physical dependence. However, both drugs produce tolerance, meaning that people who take the drug repeatedly must take higher doses to achieve the same effect. LSD and psilocybin also produce cross-tolerance, meaning people using these drugs can become tolerant to other hallucinogens.

MDMA

MDMA has hallucinogenic as well as stimulant properties.[17] While its acute effects can last 3 to 6 hours, over the course of the week following moderate use of MDMA, an individual may experience irritability, impulsiveness, aggression, depression, sleep problems, anxiety, memory and attention problems, decreased appetite, or decreased interest in and pleasure from sex. High doses of MDMA can affect the body's ability to regulate temperature. This can lead to a spike in body temperature that can occasionally result in liver, kidney, heart failure, or even death.

MDMA can stress the heart, increasing heart rate and blood pressure, and can damage the kidneys. Animal studies show that MDMA may damage specific neurons in the brain, but research on MDMA's effects on the human brain is not conclusive at this time. However, a number of studies show that long-term, heavy MDMA use is associated with cognitive deficits, including problems with learning and memory.

Research on whether MDMA is addictive is inconclusive. Experiments have shown that animals will self-administer MDMA – an important indicator of a drug's potential for misuse – although to a lesser degree than some other drugs of abuse, such as cocaine. In addition, the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) notes that over 50 percent of heavy MDMA-using adults continue use despite physical or psychological problems, tolerance, hazardous use, and spending a great deal of time obtaining MDMA. Some individuals report withdrawal symptoms when discontinuing use, including fatigue, loss of appetite, depression, and trouble concentrating.

Ibogaine

Ibogaine is a naturally-occurring substance that can induce long-lasting alterations in perception, emotion, and cognition, with elements of hallucination and sensory hypersensitivity following oral ingestion. It acts on pathways known to be affected by opioid addiction and has been claimed to reduce craving and relapse in patients with substance use disorder. There have been isolated reports of HPPD (similar to LSD and psilocybin) arising in individuals taking sufficiently high doses. At the current time, there is no evidence that ibogaine is addictive.

4. Is the FDA petitioning to reclassify any psychedelic drugs from schedule I drugs to schedule IV drugs?

As mentioned above, a drug must have a currently accepted medical use in the United States to be eligible for placement in Schedule II, III, IV, or V through the administrative drug scheduling process (21 U.S.C. 812 (b). FDA is not currently recommending a transfer of any Schedule I psychedelic drugs to any of the schedules applicable for drugs having a currently accepted medical use in the United States.

[17] https://www.drugabuse.gov/drugs-abuse/mdma-ecstasymolly

Drugs must be investigated rigorously prior to submission for FDA approval for a proposed therapeutic use. The evidence collected regarding the drug's therapeutic efficacy, as well as data that thoroughly characterizes the drug's safety, including data pertaining to its abuse and dependence liability, is submitted to FDA in a new drug application (NDA). In parallel with its review of the NDA, FDA typically conducts a thorough scientific and medical analysis of the drug, pursuant to 21 U.S.C. 811(b). For drug applications that receive FDA approval, FDA will, in consultation with NIDA, provide the findings from its analysis to the Department of Health and Human Services, Office of the Assistant Secretary for Health (the ASH). Upon review of these findings, the ASH will transmit a recommendation to the Administrator of the Drug Enforcement Administration (DEA) as to the appropriate level of control for the drug under the CSA schedules. Once the DEA is in possession of both the scheduling recommendation from the ASH and a notification from FDA that the NDA for the drug has in fact received FDA approval, DEA will issue an interim final rule to place the drug in the schedule of control the Administrator deems most appropriate, pursuant to 21 U.S.C. 811 (a-c) and (j). Under this framework, psychedelic drugs currently controlled in Schedule I could be recommended for placement in Schedule II, III, IV, or V once receiving an FDA approval for a therapeutic use.

We greatly appreciate Congress's continued commitment to NIH and FDA to ensure that our nation remains the global leader in biomedical research and advances in human health. Please let us know if you have any additional questions.

Sincerely yours,

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Acting Commissioner of Food and Drugs

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