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Ethical Considerations Regarding Psychedelics for Clinical Pain Research

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Abstract: Psychedelics, substances with a long history of cultural and medicinal use, are experiencing a resurgence in clinical research, particularly in psychiatry. Despite their classification as Schedule I drugs, recent studies suggest therapeutic potential, particularly in treating refractory depression. With chronic pain representing a major health concern and with few non-opioid treatment options available, psychedelics are being explored as alternative treatment modalities. The National Institutes of Health (NIH) now funds psychedelic research, marking a shift from previous decades of limited funding. However, ethical considerations loom large. Vulnerable populations, such as those with chronic pain that impairs their autonomy, require careful consideration by researchers of risks and benefits. Additionally, researchers and interested entities must navigate complex regulatory landscapes involving the United States Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) when considering pursuing possible research. Furthermore, transparent collaboration among stakeholders—patients, researchers, and regulatory bodies—is crucial for participant safety and successful research. Although a number of ethical approaches can be taken, we posit that stakeholders consider utilizing principal-based research ethics, comprised of the principles of autonomy, beneficence, justice, and nonmaleficence, to guide the process. Ultimately, balancing therapeutic promise with ethical integrity is paramount. Careful planning, collaboration, and adherence to ethical principles can increase the likelihood that psychedelic research in chronic pain management progresses responsibly, offering hope for patients while safeguarding their well-being.

Keywords: ethics, psychedelics, chronic pain, research, drug enforcement administration

Introduction

Psychedelics represent a broad category of substances that have long existed on the fringe of Western clinical medicine. The term "psychedelic" was coined by psychiatrist Humphrey Osmond and is derived from the ancient Greek words psychē (translated as "soul" or "mind") and dēlein (translated as "to reveal" or "to manifest") - the word literally translates as "mind manifesting" or "soul revealing".[1] Psychedelics were used long before the industrialized world was introduced to them in 1897, when Arthur Heffter isolated mescaline from the peyote cactus. Dating as far back as 5700 years ago, these substances have been used in ancient Greece, Mexico, and India. Psychedelics still remain in use in Native American religious ceremonies and in ritual healing practices in the Amazonian Basin, amongst others.[2–8] Psychedelics enjoyed an enthusiastic interest in psychiatric research up to the late 1960s, after which cultural and political changes along with stricter regulations contributed to the decision to place psychedelics in Schedule I of the 1971 UN Convention on Psychotropic Substances, thus ceasing clinical use and leading to the abrupt decline of research funding.[1,9,10]

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Over the past decade, there has been a growing body of evidence to suggest that psychedelics may serve a growing therapeutic use in contemporary clinical practice.[10–12] One of the more common areas of clinical study regarding psychedelics is in the field of psychiatry, in which recent studies have demonstrated promising results in regard to psilocybin for use in refractory depression, with funded research exploring other indications such as obsessive-compulsive disorder and alcohol use disorder.[13–17]

In general, psychedelics not only effect a person's interoception, their sense and perception of their own body, but are substances that alter how one perceives the outside world.[18] The visual hallucinations resulting from psychedelic consumption are quite common, likely resulting from the effect on serotonin (5-HT_{2A}) receptors in the central nervous system.[18] One notable aspect of psychedelics is their potential role in promoting neuroplasticity, which may serve as a therapeutic aid.[18,19] This concept of changing the structural networks of neuron connections in the brain through single (or several) doses of psychedelic substances has led to a great interest in this class of drugs.[18] Thus, the focus of this analysis will be on the class of substances that alter perception through the 5-HT_{2A} serotonergic receptor.

There are multiple classes within the categories of psychedelics, including phenethylamines such as mescaline, the tryptamines such as psilocybin, and the ergolines such as lysergic acid diethylamide (LSD).[20] Despite the growing list of classes of psychedelics, much of the current clinical evidence and use is associated with the compound psilocybin that is naturally produced by the genus *Psilocybe*, colloquially known as "magic mushrooms".[20,21] Psychedelics, including psilocybin, are currently classified as Schedule I substances defined as having no therapeutic use by the United States Drug Enforcement Administration (DEA). Thus, any clinical research must go through the authorized channels for obtaining and handling.[22] Despite this restrictive use, there are geographic regions in the United States that have decriminalized the recreational and/or clinical use of psychedelics.[23] Although there are a number of psychedelics that are under active clinical investigation, psilocybin is one of the most studied psychedelic substances undergoing active clinical trials, which could pave the path for FDA approval.[24] Given the strong clinical interest surrounding psychedelics, it is important to keep ethical considerations at the forefront when implementing their use in research. In this article, we provide an analysis of the ethical considerations of psychedelics in clinical pain research.

Chronic Pain and Ethical Principles

Chronic pain, defined as pain that persists for >3 months, is one of the leading causes of disability in the United States, affecting between 50 and 100 million people and accounting for nearly $600 billion in healthcare costs annually.[25–27] Opioids, which were welcomed as a solution to chronic pain in the 1990s, rapidly became a double-edged sword in the United States, as the opioid epidemic took an unprecedented toll in terms of lives lost and the economic impact of addiction on the healthcare system.[28] Moreover, the use of opioid analgesics for chronic pain has been associated with opioid-use disorder and negative affective states such as depression and anxiety, as well as potential opioid-induced hyperalgesia.[29] Given the iatrogenesis of long-term opioid management, novel agents which are safe and effective are desperately needed to help benefit those in chronic pain. This need has led researchers to turn to psychedelics, and recent preliminary studies have suggested some potential for the role of psychedelics in the management of chronic pain and headache.[30,31] Since 5-HT receptors are involved in the pain processing pathway and their activation results in the inhibition of pain, the partial agonistic properties of psychedelics may lead to pain modulation and reduction.[30,31]

Although there is a lack of published literature on the ethics of psychedelics in the field of clinical pain research, there are published ethical guidelines and principles for the study of psychedelics in psychiatry.[32] These ethical principles do have some crossover and relevance in the field of pain medicine, and utilization of these guidelines can help those exploring novel chronic pain management modalities implement psychedelics in a way that targets maximum benefit for participants. Furthermore, while psychedelic clinical research can be performed, it does not mean that it should be if it will not be to the advantage of those who suffer from chronic pain. This ties into the existing ethical structure of the Nuremberg Code of Ethics, which reminds physicians and clinicians that the results of any proposed study should be meaningful and helpful to a portion of society and not simply research that is conducted for the sake of completing research.[33]

In this article, we will examine the use of psychedelics for clinical pain research through the lens of four ethical principles.[33] This ethical framework encompasses beneficence (the effort to promote good), non-maleficence (the measures

taken to avoid harm), autonomy (the right to self-govern), and justice (fairness and equality in subject selection and distribution of benefits and burdens).

Beneficence

Chronic pain clinical researchers utilizing psychedelics should prioritize beneficence to ensure that research contributes positively to society and the well-being of individuals. "Research for the sake of research" is a violation of not just beneficence but also nonmaleficence, as there is potential for such investigation to be deleterious to patient/subjects while concomitantly providing little, if any, patient/subject benefit. How our investigation will aid our participants must be at the forefront of our decision making as psychedelics research could lead to many medical strides including the treatment of difficult to manage conditions such as complex regional pain syndrome and neuralgiform headaches.[34,35] Although ethical violations associated with exploratory research without a direction are certainly not unique to the study of psychedelics in pain management, the serious risks associated with psychedelics in conjunction with limited empirical evidence to date in ameliorating chronic pain creates the potential for disregarding the principle of beneficence.

If this principle is not upheld, it could severely impact public trust in supporting future endeavors and sow skepticism toward the medical community. Psychedelic research for chronic pain should be guided by the principle of beneficence to ensure that studies are conducted ethically and responsibly, fostering advancements that are not only scientifically sound but also socially beneficial.

Non-Maleficence

When utilizing psychedelics in chronic pain management research, it is crucial we ensure that harm is not done to participants. At this time, psychedelic research is being funded through the National Institutes of Health (NIH) for a variety of clinical applications.[36] This is a relatively new development, as federal funding dwindled after the Controlled Substances Act of 1970 classified psilocybin, the main psychoactive constituent of psychedelic mushrooms, as a Schedule I drug.[36,37] Furthermore, there is a growing prevalence of recreational use of hallucinogens in the United States. The incidence of young adults aged 18–25 who have used a hallucinogen within the past year may now be above 7%.[38]

With the resurgence of interest in psychedelics both recreationally and as a tool in research, it is vital to be conscious of the lessons learned from previous research to ensure that current study designs and protocols in human participants adhere to ethical standards.[39] Egregious violations of ethical protocols, such as lack of informed consent in some cases, in military or intelligence agency-supported research, has resulted in enduring harm to some participants.[40] Moreover, unsupported claims regarding purported benefits of psychedelics, and at times, explicit encouragement for non-clinical use by some members of the research community may have resulted in uncontrolled recreational use. Infamously, Timothy Leary, leader of the controversial Harvard Psilocybin Project, was known to instruct the youth of the 1960s to "Turn on, tune in, drop out".[41]

Furthermore, it is essential to remain cognizant that patients participating in studies involving psychedelics for chronic pain research often have significant comorbidities (severe anxiety, depression, opioid use disorder, or post-traumatic stress disorder), and thus, these populations are vulnerable, particularly when they have failed numerous conservative therapies and are desperately looking for hope in experimental treatments. This subject population requires special attention to ensure that they are aware of the experimental nature and potential risks of psychedelics as a treatment modality. Moreover, reinforcement and adherence to the screening process to identify appropriate patient candidates for such studies becomes even more crucial.[42] Participants must understand the possibility of ending studies early and why and what their rights are if they believe themselves injured in a study.

As psychedelic use is a relatively controversial subject, it is vital that researchers continue to examine it from an ethical perspective, addressing factors including increased attention in the media, public perception, ongoing changes in laws regulating their use in the United States, and the wide range of potential side effects including hallucinations, disorientation, and self-harm.[42]

Although these side effects may seem severe and possibly associated with stigma at first glance, some of these side effects can occur with other pain-relieving medications, as well. This counterpoint needs to be considered in the ethical approval process of such clinical research. Additionally, research has demonstrated that the anecdotal side effects of psychedelics may

be overly dramatized, and that they may in fact be safer than perceived when the research is approached in an ethical, evidence-based manner.[42] Most importantly, there are very few studies on the effects of psychedelics on chronic pain, and a discussion concerning their ethical use in clinical research is therefore very timely and necessary as the FDA requires input from both the medical/scientific community and the public.[31,43] Proper discourse with accessible evidence is needed to avoid the derailment of a potential new class of therapeutics to aid in the treatment of chronic pain.[44] As a result, researchers serve a crucial role, in that they are responsible for properly setting up clinical studies to minimize all possible risks and having a mitigation strategy to deal with any adverse events that develop.

As use of psychedelics in clinical investigation continues to develop, it will require careful consideration and acceptance by federal and institutional regulatory bodies involved in the review process in order to ensure participant safety, such as the FDA, DEA, and Institutional Review Boards (IRBs) and Data Safety and Monitoring Committees. Acceptance by the FDA requires the submission of an Investigational New Drug Application (IND). The sponsor of the IND accepts responsibility and initiates the clinical investigation and may be an individual, company, government agency, academic institution, or other organization.[45] Regardless of sponsor type, the required components of an IND remain the same, and psychedelics, as well as other Schedule I drugs, can be used for research only with a DEA license/registration via DEA Form 225.[46] Researchers are required to secure IND acceptance and IRB approval prior to applying for this licensure, serving as another measure to help participants avoid harm.

The DEA and FDA communicate throughout the DEA registration process, which is described in FDA's Manual of Policies and Procedures from the Center for Drug Evaluation and Research section 4200.1.[47,48] The site and investigator, for handling the investigational drug, both need to be registered by the FDA. Notably, physical inspections are mandatory. If a clinical site already has the requisite Schedule I licensure, the DEA review period typically requires 4–12 weeks. Clinical sites that do not have the requisite licensure can expect delays.[49] Therefore, it is recommended that researchers utilize the Schedule I Researcher Pre-Application Checklist located at the Department of Justice webpage for DEA Forms and Application to assist with the process.[48]

While federal organizations have taken measures to help ensure that harm is minimized, psychedelics are still potentially associated with considerable risks such as hallucinations, and empirical investigations that include psychedelics may be contra-indicated for healthy individuals. Most studies include some "at-risk" population, which is necessary to determine whether psychedelics produce any clinical improvements. These at-risk populations may have a chronic pain diagnosis, psychiatric diagnoses, and/or substance use disorder diagnoses that affect their decision-making capacities.[50] Researchers should do whatever is possible to ensure that potential risks and harms are minimized to whatever extent possible, and that study participants are able to consent for themselves and have decision-making capacity, as well as appropriate mental status for study participation.

Although the side effect profile of psychedelics cannot be ignored, they are still reasonable investigational drugs for clinical research given the benchmarks that psychedelics potentially meet for value to those who are involved.[51] Psychedelics can be given in a single dose and have long-lasting results, therefore producing a reasonable risk to benefit ratio.[14,31,51] Psychedelics are also not known to cause significant (or any) addiction potential or dependence and may represent a significant net value to certain patient populations.[20,51] Through proper regulation and research design, harm can be minimized thus allowing participants to partake in chronic pain research utilizing psychedelics in the safest fashion possible.

Autonomy

To guarantee that research participant autonomy is upheld, it is essential that there be mutual respect between the study participant and the research team, as they are technically agreeing to mutually assume the risks of participating in a clinical study involving a substance that is banned outside of research trials.[51] Informed consent is pivotal to providing that autonomy and respect.[52] The integrity of the informed consent process is crucial, as participants may be very new to the concept of psychedelics. Prior research has demonstrated that consenting earlier in the process can yield improvements in satisfaction for participants, and involving other family members in the process (as the participant allows) can increase family satisfaction by reducing their anxiety, as well.[53] The clinical research team may become very comfortable with the potential risks, and often this comfort may lead to the failure to address important aspects of the study or potential risks because they incorrectly assume that these facts are common knowledge. It would be prudent to have study participants quizzed–repeating back to the clinical research team what they perceive as the purpose of the study, its

risks, their rights and the parameters of their involvement as a study participant. This is especially key in psychedelics research, which pose the unique risk of a shift in personality and values as well as the rare risk of mental health risks such as psychosis.[54] In an ideal setting, the clinical team would return on a separate occasion, after the consent was obtained but before the study has commenced, to determine whether any new questions arose following the initial discussion. The study team member who is obtaining the consent should not be a physician who is already treating the participant and has developed a patient-physician therapeutic relationship with the participant, as the relationship may cause the participant to feel an unconscious need to enroll in the study, even if only minimally interested.[55] As a study proceeds investigators must be alert to reconsent as data is collected and to share study results with participants when research concludes.

An alternative method for obtaining informed consent is the two-stage process which can assist in managing information overload, decisional anxiety, and overall burden.[56,57] In the initial stage, participants are invited into the study and the research procedures and questionnaires are explained, and, if they are comfortable, will sign the initial consent.[56,57] The participants are then informed of the possibility of being randomly selected for the experimental arm, or, if they decline once selected, they have the option of receiving the standard of care.[56,57] Those selected for the experimental arm who agree to participate are then informed of the experimental treatment and asked to sign the second consent.[56,57] With the intent-to-treat, the participants can then be analyzed irrespective of whether they choose to enter the experimental arm of the study or receive stand care treatments.[56,57] Through mutual respect between researchers and participants, and ensuring proper informed consent, autonomy can be upheld and maintained.

Justice

The principle of justice is necessary to ensure fairness in the selection of participants such that every potential participant is treated equally. To facilitate this, studies should require a full board review by its IRB.[58] The complexities of an IRB submission that involve a clinical trial or a patient safety issue are common reasons for delays of IRB approval.[59] Researchers need to have in place a proper timeline drafted for completion of the IRB submission and study protocols, federal investigational drug applications, and the study itself. A data safety monitoring board is important to establish in order to periodically assess adverse events or complications and significant trends as evidence accumulates.

The IRB review assures the rights and welfare of human subjects, primarily achieved by obtaining informed consent, minimizing risks, and guaranteeing a standardized process among research participants. Due to the unpredictable effects and ethical implications of research with psychedelics the elements and continued communications with the IRB is vital. Investigators experienced in conducting clinical trials using psychedelics are likely to discuss in their proposal several ways to minimize risks, such as including appropriate screening criteria, implementing an enhanced informed consent process and adequate preparation for the treatment period, as well as establishing touch boundaries.[54,60]

A reasonable recommendation would also include the formation of a psychedelic clinical research workgroup to partner with the IRB to establish that all stakeholders are involved in an ethical process. The inclusion of peoples' suffering from chronic pain in such a workgroup would also bolster justice within the studies as they could provide their own unique perspective, such as an understanding of the degree of risk they are willing to take to trial an experimental substance.

For a relatively new drug class such as psychedelics to successfully navigate an ethical and reasonable IRB process, multiple meetings and discussions involving the research and IRB teams prior to final IRB submission would likely be prudent. Such open dialogue and communication between the IRB and the research team could help clarify any confusion pertaining to ethical considerations or concerns and could allow the research team to demonstrate its mastery of the scientific background knowledge related to the proposal.[61] There would likely be numerous components and certifications, both on a local and federal level, prior to such a clinical trial being able to be initiated, and involving the IRB early to help navigate this process could help avoid ethical as well as practical conundrums.

When applying justice, there is also the concern that psychedelics are currently cost-prohibitive for research studies due to regulations, and there may be significant financial gain for companies that produce and manufacture these products.[62] These companies are technically providing a substance that is federally banned outside of research studies and is therefore highly regulated and controlled. However, the companies have an incentineve to sell more product, and they may willingly provide psychedelics even if they are unclear of the clinical benefit, research purpose, or exact study design. Psychedelics are still considered illegal in most regions of the country, including on a federal level. This creates a degree of ambiguity

regarding the utilization of psychedelics in clinical research in the first place, not particularly different from ethical concerns and the ambiguity regarding medical cannabis, which is also a heavily regulated Schedule I substance that has been deemed by federal agencies to have no therapeutic purpose, although it may soon be reclassified.[63]

Therefore, the institution, study team, and other stakeholders would ideally and carefully vet any potential conflicts of interest that could interfere with objectivity. A study that demonstrates a clinical benefit of psychedelics for chronic pain could receive considerable attention in the lay press, and this could backfire if it were later determined that an investigator or stakeholder had a potential financial gain due to the study results. Of course, all study teams should carefully analyze conflicts of interest, but experimental substances such as psychedelics being investigated in extremely vulnerable populations, such as refractory chronic pain patients, require an even higher level of due diligence.

For psychedelic clinical research to be able to provide equal benefit to different populations, it is also important that it be generalizable. In the field of psychiatry, a risk exists such that patients or providers may misinterpret data from research using psychedelics to seem exceedingly beneficial or broadly impactful, and this risk would be similar in the field of chronic pain.[32] Generalizability is crucial, as participants that are involved in the trial or patients who read about the results of the trial may assume that psychedelics are safe for recreational use or use outside of any clinical supervised research study. Conspicuously, this could have negative consequences, and is also federally illegal for recreational or therapeutic use (outside of an appropriate clinical trial) as a Schedule I drug.[22] By ensuring that justice is respected when using psychedelics in chronic pain research, investigators can reduce adverse events, thereby also demonstrating respect for the principle of nonmaleficence.

Furthermore, the Belmont Report addresses the ethical guidelines of helping patients in a positive way.[64] Its focus is on justice as an ethical principle, as marginalized and forgotten groups should benefit from research.[64] Patients with chronic pain often feel judged by society, marginalized, and have struggled with substance use disorders, depression, anxiety, or even suicidal thoughts in the past which similarly have been stigmatized and exacerbate their sense of being ostracized. It is paramount that research pain management using psychedelics is conducted in a manner that is inclusive to all populations and is working for the benefit of all people.

Conclusion

The field of therapeutic psychedelics holds promise for offering alternative options for patients with chronic pain. However, if these potential clinical benefits of psychedelics are not first disentangled from potential ethical imbroglios through careful planning, it may lead to significant downstream effects for all stakeholders. To ensure that research progresses ethically, it is essential to uphold the four principles of beneficence, non-maleficence, autonomy, and justice throughout the process. A thorough ethical assessment, guided by these principles and in strong collaboration with all stakeholders, including IRBs, will help address potential ethical dilemmas before they arise. This approach will allow research to develop in a manner that is ethical, moral, and maximally benefits our patients, our study participants, and society.

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