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Psychedelic treatments for mental health conditions pose challenges for informed consent

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Enhanced informed consent procedures are needed for patients treated with psychedelics such as psilocybin and MDMA, due to effects that include an altered state of consciousness and vulnerability to suggestion.

In past years, clinical trials with psychedelic substances have been conducted to find alternative treatments for hard-to-treat mental health conditions such as treatment-resistant depression[1], cancer-related depression and anxiety symptoms[2] and post-traumatic stress disorder[3]. Clinical research has advanced under the regulation of national ethical and medication authorities for clinical trials, much as for any study testing a new intervention. Indeed, recent research on psychedelics has been conducted under the protected conditions of clinical trials, following international guidelines. However, psychedelic treatments present unique ethical and regulatory challenges that may not have been fully addressed within the traditional structures of clinical trial regulation[4]. These challenges need to be addressed before these substances are approved for use in general clinical practice.

Psychedelic therapies

Psychedelics such as lysergic acid-*N*,*N*-diethylamide (LSD) and psilocybin are serotonergic agonists, with acute psychoactive effects on perception and mood, along with several other cognitive processes. In clinical research, other substances sharing some of the psychoactive effects of psychedelics, such as ketamine and 3,4-methylenedioxymethamphetamine (MDMA), frequently designated as atypical psychedelic substances, are also being tested (Table 1). Although atypical psychedelics also induce altered states of consciousness, they are distinct pharmacologically[5] and induce a qualitatively distinct subjective experience.

Generally, typical and atypical psychedelic drugs are considered physiologically safe and have limited abuse liability. Unlike other pharmacological interventions, they are often administered in combination with some form of psychological support or psychotherapy. This is done for safety reasons[6], as the induction of an altered state of consciousness requires supervision. However, it is also thought that the psychological intervention may be critical to modulate the subjective experience associated with the drug and enhance its clinical efficacy[2]. In many cases, a specific and/or manualized psychotherapy intervention accompanies the psychedelic drug administration, which includes sessions of preparation, integration and varying levels of guidance during the subjective experience. It is also possible that psychedelic treatments may be effective irrespective of the application of any form of psychotherapy, but there is limited empirical research to address this possibility.

Efficacy for mental health disorders

In the field of psychedelic treatments, psilocybin has been one of the most studied substances. This is a naturally occurring psychedelic compound produced by several species of fungi, often called 'magic mushrooms'. Synthetic psilocybin has been shown to reduce symptoms of depression and anxiety related to cancer diagnosis[2], as well as major depressive disorder and treatment-resistant depression[1,7]. The therapeutic use of psilocybin has also been explored for obsessive compulsive disorder[8], eating disorders[9] and nicotine or alcohol use disorders[7]. Treatment with psilocybin has been applied individually as well as in group settings, which may reduce costs associated with psychological support provided before, during and/or after drug administration[6].

Another well-studied compound is MDMA, with results showing that it may be an effective treatment for post-traumatic stress disorder[3] by reducing associated symptoms, as well as for social anxiety in autism spectrum disorder and for alcohol use disorder[7]. Ayahuasca, containing a mixture of *N*,*N*-dimethyltryptamine and a monoamine oxidase inhibitor, with typical psychedelic effects, has also been tested for treatment-resistant depression[10] and substance use disorder[11], while

Table 1 | Main typical and atypical psychedelics used in clinical trials

Compound	Mechanism of action[5]	Indications being tested[7]
Ayahuasca (mixture of *N*,*N*-dimethyltryptamine and monoamine oxidase inhibitors)	*N*,*N*-Dimethyltryptamine is a classic psychedelic, acting as an agonist of 5-HT_{2A} receptors, and also has affinity for other receptors such as 5-HT_{1A}. It escapes peripheral inactivation via effects of monoamine oxidase inhibitors.	Major depressive disorder and treatment-resistant depression[10]; substance use disorder[11]
Ketamine	Dissociative acting primarily as an *N*-methyl-D-aspartate glutamate receptor antagonist.	Treatment-resistant depression; substance use disorders
LSD (lysergic acid-*N*,*N*-diethylamide)	Classic psychedelic acting as an agonist of 5-HT_{2A} receptors. It is also an agonist of most other human 5-HT receptors, as well as D1, D2, D3 and D4 DA and α1- and α2-adrenergic receptors.	End-of-life anxiety; substance use disorder[11]
MDMA (3,4-methylenedioxymethamphetamine)	Acting through induction of release and reuptake inhibition of presynaptic 5-HT, DA and noradrenaline[15].	Alcohol use disorder; post-traumatic stress disorder; social anxiety (in autism)
Psilocybin	Prodrug of psilocin, into which it is dephosphorylated in vivo and which then acts as a classic psychedelic (5-HT_{2A} receptor agonist) and is also a potent agonist for many other serotonin receptors, including 5-HT_{1A}, 5-HT_{2B} and 5-HT_{2C}.	Cancer-related depression and/or anxiety symptoms; eating disorders[9]; major depressive disorder and treatment-resistant depression; obsessive compulsive disorder[8]; substance use disorders

Mechanisms of action are presented as detailed by Kwan et al.[5], except where noted. Tested indication are presented as reviewed by Cavarra et al.[7], except where noted. 5-HT, 5-hydroxytryptamine (also known as serotonin); DA, dopamine.

the clinical potential of LSD has been investigated to reduce end-of-life anxiety and also to treat substance use disorders[7].

Ketamine is an *N*-methyl-D-aspartate glutamate receptor antagonist with dissociative effects, approved for medical use as an anesthetic. Its use in the treatment of psychiatric conditions is increasingly considered under the umbrella of psychedelic treatments. Ketamine has been studied to treat opioid use disorders and to reduce symptoms of depression[7]. So far, it has mostly been tested in the absence of formal adjuvant psychological support and/or psychotherapy[12]. However, there is some evidence to suggest that adding a psychotherapeutic component, such as adjuvant or follow-up treatment, may prolong ketamine's antidepressant effect[13]. In contrast to typical psychedelics, ketamine is available as an anesthetic, and it is being offered off-label for psychiatric indications. However, specific professional medical or psychological guidance regarding off-label use of substances with acute psychoactive effects, such as ketamine, are currently lacking. In 2019, esketamine, the *S*-enantiomer of ketamine (itself a racemic mixture), was approved in the form of a nasal spray to treat treatment-resistant depression in combination with an oral antidepressant, first by the US Food and Drug Administration (FDA) and later by the European Medicines Agency (EMA). Esketamine is used as a hospital-based treatment under medical supervision, but there are no recommendations regarding adjuvant psychological support[14]. Access to such treatment is substantially limited in most countries.

Impaired decision making

Research on the therapeutic use of psychedelics has also addressed their safety. Mostly mild to moderate and transient adverse events, such as anxiety, headache and altered sense of reality, among others, typically occurring during and immediately after the drug administration sessions, have been described. Recently, concerns about the potential for more severe adverse events were raised from the results of the largest multicenter randomized controlled trial published to date, testing the efficacy of a single dose of psilocybin for treatment-resistant depression. Suicidal ideation and intentional self-injury were reported in the groups treated with the highest doses of psilocybin, but were absent in the group treated with the lowest dose[1]. Although these differences were not statistically significant, they imply the need for caution in the future development of this treatment.

It is good standard clinical practice to discuss safety issues and adverse events during informed consent procedures before starting treatments. Obtaining informed consent in psychological interventions also includes explaining associated risks and harms, defining the treatment setting and goals, and discussing existing evidence about the treatment. In addition, informed consent, particularly in psychotherapy, is an ongoing process to which patient and therapist agree at the beginning of the therapy. During treatment, the patient is expected to be autonomous in decision-making processes, and treatments can be adjusted, for example, in consideration of treatment goals or setting. In psychedelic treatments, this procedure is complicated by the patient being in an altered state of consciousness after drug administration, rendering the most common informed consent procedures potentially insufficient. The expected effects of being in an altered state of consciousness, and its consequent changes in behaviors and feelings, need to be fully disclosed and discussed in detail with patients during the initial informed consent procedures.

In a recent paper, Smith and Appelbaum present a discussion of the ethical challenges with informed consent procedures for psychedelics[4]. It is challenging to prepare the patient for the ineffable quality of the psychedelic experience and the difficulty of aborting a session once the substance is ingested. In addition to agreeing on relatively standard procedures, including the potential need for rescue medication, such as anti-psychotics in the case of agitation, patients will need to understand that, once they begin experiencing psychedelic effects, their frame of mind can change in ways that may lead to the wish to remove consent, and/or to a decision not to provide consent if those effects had been anticipated[4]. Full disclosure and agreement regarding the applied intervention techniques must be guaranteed, such as the possible use of touch and other grounding techniques, and consent given by the patient not only prior to the use of those techniques, but before the psychoactive substance is administered. Importantly, although these thorough procedures for informed consent may be guaranteed in the context of clinical trials, they can be challenging to implement in everyday clinical practice.

Heightened suggestibility

A central challenge that must be anticipated for a dosing session is how to deal with a change of opinion or attitude regarding the use of touch. A potential effect of psychedelic substances that is of particular relevance is heightened suggestibility, which may increase vulnerability to potential abuse. Even in the absence of psychedelics, psychological interventions may be prone to boundary transgressions due to the development of a trusting relationship between patient and therapist. The extent to which suggestibility and vulnerability may be enhanced in a psychedelic setting, through the drug-induced altered state of consciousness, should not be underestimated. The patient should be informed about the possibility of feeling closer or more familiar to the therapist when under the influence of the substance. Ultimately, the therapist or equivalent, rather than mitigating psychological risks associated with the psychedelic experience, can be the agent of a boundary transgression. Information regarding the nature of this increased vulnerability of the patient must be provided as part of enhanced informed consent procedures.

In addition to optimizing informed consent procedures, using the right settings for psychedelic treatments has also been considered as a means to enhance safety for patients under altered states of mind. As with esketamine, for most research with ketamine, the choice has been standard medical supervision of the administration processes in hospital-based practice. For other psychedelics, however, research has typically been conducted with some form of specialized psychological support or psychotherapeutic intervention, sometimes in non-hospital clinical settings. Differences in safety between these two alternatives, and any associated advantages, for example in regarding efficacy, should be further explored. Nevertheless, standard safety settings for the administration of medication with acute mind-altering effects, such as those in place for esketamine[14], should be considered for other psychedelic therapies, unless future research makes it clear that they are unnecessary or present major disadvantages for efficacy.

It has also been hypothesized that adjuvant psychotherapy can influence expectation and enhance the psychedelic experience, possibly leading to more significant clinical benefits. Indeed, the authors of this Comment believe that the need for and impact of adjuvant psychological interventions should be tested in regard to not only the safety of the intervention but also the clinical efficacy. If unequivocal evidence of advantages to the use of psychological interventions during the psychedelic experience is produced, additional and specific technical guidance and professional regulation will certainly be necessary. Mental health providers will need to be given the technical and ethical tools to prepare for and conduct psychological processes with patients under acute altered states of consciousness and during their aftereffects. Importantly, regional, national or transnational (such as the European Union) professional boards of psychiatrists and clinical psychologists must work jointly toward professional regulation of psychedelic treatments and the development of robust risk management plans that consider standard medical supervision, as detailed above.

Lack of standardized protocols

Growing attention to promising clinical results of psychedelic treatments are bringing important ethical and policy challenges to the field of mental healthcare. Currently, the field does not have a unified and empirically informed administration protocol and setting for each of these substances. Regulatory agencies, such as the EMA in Europe, the FDA in the USA and others elsewhere, are well positioned to contribute toward the standardization of protocols for psychedelic treatments, such as dosage, administration setting and participating health professionals, in addition to the development of an informed risk management plan, akin to the FDA risk evaluation and mitigation strategies. Regional and national ethics boards should also have an active role in developing informed consent guidelines. Finally, professional credentials to work within psychedelic treatments should be regulated. It is well known from other contexts in mental healthcare that professional training qualifications with qualified supervision help protect patients. Medical and psychological professional boards and societies must be involved in defining the procedures, expertise and qualifications of the professionals participating in psychedelic treatments.

Overlooking the ethical, regulatory and policy challenges that are anticipated for psychedelic treatments (Table 2) could risk halting implementation and research in the field. The development of policy and regulation for such treatments will necessarily be complex and

Table 2 | Summary of ethical, regulatory and policy challenges around psychedelics and their potential solutions

Challenges	Solutions

Altered state of consciousness during psychedelic experience, with consequences that are difficult to explain and anticipate	• Obtain initial informed consent prior to administration of the psychoactive substance:
	  • Full disclosure and detailed discussion of the potential effects of the psychedelic experience on autonomous decision-making and on possible wish to remove consent, and/or not to provide consent, if those effects had been anticipated;
	  • Full disclosure on potential need for rescue interventions, such as anti-psychotics for agitation, in the absence of added consent;
	  • Agreement on possible intervention techniques, such as touch and other grounding techniques, and the need for added consent.
	• Application of intervention techniques during the psychedelic session, as per informed consent, and with added consent prior to their use.

Enhanced suggestibility and vulnerability in the psychedelic setting	• Initial informed consent procedures should include informing patients about the possibility of feeling closer or more familiar to clinicians, and potential impact on vulnerability to abuse. • Professional oversight from regulatory agencies and professional associations.
Implementation of thorough procedures for informed consent outside clinical trials	• Formal regulation and oversight of informed consent procedures from ethical authorities, regulatory agencies and professional associations.
Definition of optimal clinical setting for psychedelic treatments	• Favor hospital-based setting under standard medical supervision for the psychedelic session. • Regulatory agencies and other authorities should consider other alternatives, such as a non-hospital setting, if equivalent safety and improved efficacy is clearly demonstrated.
Definition of optimal therapeutic procedures for psychedelic treatments	• Apply treatments during psychedelic session as per procedures with best available evidence to date. • Regulatory agencies and other authorities should define and regulate therapeutic procedures for psychedelic treatments and should support safety and efficacy assessment of specific procedures, such as psychotherapy. • Professional associations for psychiatry, clinical psychology and nursing should provide joint professional regulation with specific technical guidance, training, certification, supervision and oversight.

will require joint efforts from regulatory agencies, ethical authorities, and scientific and professional societies, working together with policy-makers, to ensure the safety and well-being of patients.

In Portugal, researchers involved in trials with psychedelics are collaborating with local scientific and professional societies of psychiatrists and psychologists, as well as members of a national ethics authority, to anticipate the regulatory challenges expected if such treatments become available. This paper reflects the first product of this collaboration, which may provide a model for other countries as they prepare for the implementation of psychedelic treatments in clinical practice.

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