Ethics and ego dissolution: the case of psilocybin

William R Smith,[1] Dominic Sisti[2]

[1]Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
[2]Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

Correspondence to
Dr William R Smith, Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19083, USA; William.Smith@pennmedicine.upenn.edu

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ABSTRACT

Despite the fact that psychedelics were proscribed from medical research half a century ago, recent, early-phase trials on psychedelics have suggested that they bring novel benefits to patients in the treatment of several mental and substance use disorders. When beneficial, the psychedelic experience is characterized by features unlike those of other psychiatric and medical treatments. These include senses of losing self-importance, ineffable knowledge, feelings of unity and connection with others and encountering 'deep' reality or God. In addition to symptom relief, psychedelic experiences often lead to significant changes in a patient's personality and worldview. Focusing on the case of psilocybin, we argue that the peculiar features of psychedelics pose certain novel risks, which warrant an enhanced informed consent process–one that is more comprehensive than what may be typical for other psychiatric medications. We highlight key issues that should be focused on during the consent process and suggest discussion prompts for enhanced consent in psychedelic psychiatry. Finally, we respond to potential objections before concluding with a discussion of ethical considerations that will arise as psychedelics proceed from highly controlled research environments into mainstream clinical psychiatry.

Early-phase trials with psilocybin-assisted psychotherapy suggest it provides sustained symptom-reduction for treatment-resistant depression (TRD) as well as for cancer-related depression and anxiety.[1–5] Additionally, early studies with psilocybin for smoking and alcohol cessation have shown promising results.[6–8] Moreover, psilocybin appears to be safe, with very few adverse events.[9] Likewise, trials with 3,4-methylenedioxmethamphetamine (MDMA) for social anxiety in patients with autism[10] and for post-traumatic stress disorder[11 12] as well as those with lysergic acid diethylamide (LSD) for anxiety[13] and ayahuasca for TRD[14] have also yielded promising results. Additional clinical trials are currently underway, aiming to replicate some of these findings,[15 16] and more are likely to follow. In short, psychedelics have returned to psychiatric research, despite having been banished half a century ago. Widespread clinical use may soon follow.

The therapeutic potential of psychedelics appears to be related to the peculiar, so-called 'mind-manifesting', experiences they tend to induce in the subjects that benefit. In the case of psilocybin, the characteristic experiences reported by subjects include a sense of new, ineffable knowledge, feelings of unity and connection and encounters with 'deep' reality or God. Subjects who benefit also tend to experience a sense of loss of self, or at least of self-importance, that researchers describe as 'ego dissolution'. These effects are often characterised as 'mystical' and are associated with the therapeutic benefits of psilocybin[3] and changes to personality broadly understood.[17]

Yet, despite its recent renaissance, significant benefits and potentially personality-changing mechanisms, psychedelic psychiatry has attracted very little attention among medical ethicists. Others have considered the possibility of psilocybin and MDMA for moral enhancement[18] and couple's therapy.[19] Still others have considered the ethics of newly proposed, early research on psilocybin as a proposed aid in recovery from disorders of consciousness.[20] In contrast, and notwithstanding insights by Johnson *et al*,[9] we believe that the most pressing and underexplored questions regarding psychedelics concern the established and growing work in psychiatry pointing to the potential for widespread use and benefit.

In this paper, we partially fill this gap in ethical analysis. We focus on the case of psilocybin as one of the most well-researched psychedelics. We argue that psilocybin's properties may pose novel risks—such as potentially undesirable personality changes or trauma re-exposures—as well as novel benefits. We recommend guidance for informed consent in light of such risks in both research and clinical contexts. In particular, we believe that an enhanced consent process—beyond that of typical consent in medicine—is critical. After responding to potential objections, we conclude by addressing ethical challenges that will arise as psilocybin moves from well-controlled clinical trials to clinical practice.

Before proceeding, two clarifications about terms are necessary. First, there is debate about the use of term psychedelic. Some prefer to restrict it to the 'classic' or serotonergic psychedelics, such as psilocybin, LSD, ayahuasca and ibogaine, which are thought to share a mechanism of action.[21 22] Yet, others would understand the term 'psychedelic' more broadly to include any substances with 'mind-manifesting' properties.[23] While we focus on psilocybin, we believe that our analysis generally applies to other interventions with serotonergic psychedelics. Thus, for ease of reference, we will use the term psychedelic to refer to this class in the following. Some of our points below may further generalise to interventions with non-serotonergic substances that might be called psychedelics, such as MDMA, but a full discussion of these issues is beyond our scope here.[i]

[i]As is use of psilocybin and MDMA for couples' therapy, which has been proposed for research by ethicists,[19] but is not yet as well-researched. Of note, this proposal raises particular questions regarding how to extrapolate our recommendations about consent here for two reasons. First, there are differences between MDMA and psilocybin regarding brain mechanism and the subjective state they induce. Second, there are complications that arise in

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Table 1 Defining features of the factors in the Five-Factor Model (adapted from McCrae and John[28])

Extraversion	Agreeableness	Conscientiousness	Neuroticism	Openness
Talkative	Appreciative	Efficient	Anxious	Artistic
Assertive	Not critical	Reliable	Thin-skinned	Introspective
Rapid personal tempo	Giving	Productive	Worrying	Curious
Gregarious	Generous	Not self-indulgent	Tense	Insightful
Enthusiastic	Altruistic	Dutiful	Vulnerable	Original
Warm	Trusting	Aspiring	Self-pitying	Judges in unconventional terms
	Straightforward	Disciplined		

Higher scores on a given factor are associated with the relevant defining features, whereas lower scores are associated with opposing features.
For more extensive discussion of the Five-Factor Model, to which we are indebted, see McCrae and John.[28]

Second, as noted above, personality change will be central to our discussion here, but the notion of personality is vague. Here, we will use the term broadly to refer to, roughly, the narrative features and values of an agent that make them a distinctive (type of) person. Our choice is supported in part because the term 'personality,' understood broadly, accommodates a variety of patient traits effected by psilocybin. This broad sense of personality is common in lay English discourse—even if less specific than some usage in the psychology literature. When asked to describe a friend's personality, we might appeal to their love of certain activities and the importance they place on certain relationships or organisations. Likewise, we might contrast this with another's personality by appealing to her care for her family, her love of wine and her concerns for the world and her country with that of another who is happily single, more individualist and prefers soft drinks. This broad usage admittedly compromises specificity that comes with the notion(s) employed by the psychology literature, but as we will see below, psilocybin-assisted psychotherapy is associated with these kinds of ethically important changes.

PERSONALITY CHANGE AND NEUROBIOLOGY OF PSILOCYBIN-ASSISTED PSYCHOTHERAPY

Psilocybin's therapeutic benefits have been best studied in the cases of anxiety and depression in terminal illness as well as TRD. Hence, we will focus on these cases, noting that not all changes may generalise to other therapeutic targets or other dosing strategies, such as 'micro-dosing'. In these studies, therapeutic benefit is associated with the mystical features of the psychedelic experience. These are assessed as a function of several features, including feelings of internal and external unity, sacredness, positive mood, transcendence and ineffability.[3] Similar associations have been found between the therapeutic benefit and feelings of 'oceanic boundlessness', including 'experience of unity, spiritual experience, blissful state, insightfulness and disembodiment'.[24] Notably, not all subjects achieve these states. Yet, doing so is correlated with the therapeutic benefits of psychedelics.[ii 3 24]

Further, in several studies, most subjects have ranked the psychedelic treatment with psilocybin as one of the most meaningful events of their lives.[1 3 17] They report experiences like encountering 'a great plane of consciousness' and being able to 'reach out to anybody and connect with them'.[25] Subjects also report the 'realisation that life and death are part of one circle'.[25]

Using validated instruments, such as the NEO Personality Inventory-Revised (NEO PI-R), researchers have characterised psilocybin's effects on personality according to the Five-Factor Model of personality, which describes personality in terms of openness, conscientiousness, extraversion, agreeableness and neuroticism.[26–28] (See table 1). Psilocybin decreases neuroticism and increases conscientiousness, extraversion and openness, which may be unsurprising given the profound feelings of connection during the experience.[25 26]

However, therapeutic psilocybin appears to induce personality changes, in our broad sense, beyond those clearly measured by the NEO PI-R. For instance, psilocybin augments participants' sense of spirituality.[3] Subjects report feeling deeper spirituality and being 'reborn in a way'.[25] Even participants without prior feelings of spirituality sometimes report such feelings during treatment.[29] Similarly, psilocybin appears to induce feelings of transcendence over death in patients with life-threatening cancer.[1 3]

Finally, psilocybin increases subjects' sense of connection.[29 30] Participants note profound senses of 'a greater understanding of global connectedness' and feelings that 'people, … animals, [and] … trees' are all connected. They also note deeper connections to family members—including feeling 'more emotionally open' to significant others. They feel more in touch with themselves.[25] Participants with TRD contrast this sense of connection with 'disconnection and tendency to avoid painful emotions' that they associate with previous treatments.[29]

The mechanisms and biological correlates of these experiences and changes to personality remain under investigation. Neuroimaging suggests they may involve acute decreases in functional connectivity of metacognitive centres, such as the default-mode network. These findings are associated with 'disintegration', the loss of a sense of self and an increased global connectivity that may explain reported enhanced sensory experience.[22 31 32] Notably, the metacognitive circuits reintegrate shortly after the psychedelic state—perhaps suggesting that psilocybin works in part through restructuring pathways of depression.[22 33]

Such a cognitive reset may also relate to subjects' sense of openness and connection, as might be explained by a psychodynamic interpretation, on which its benefit is mediated by enabling better access to latent thoughts. This sort of interpretation has been offered for LSD's mechanism.[34] Given the pharmacological similarities between LSD and psilocybin, the same theory might apply to psilocybin. Relatedly, interviews with patients with LSD[34] and psilocybin[29] suggest that part of the mechanism may involve altering the cognitive schema with which patients approach challenging predicaments—similar to cognitive restructuring of more traditional psychotherapies such as cognitive behavioural therapy (CBT). Other emerging evidence with ayahuasca users has suggested that psychedelics improve skills traditionally associated with other therapeutic modalities,

coordinating the psychedelic experience for multiple people which have not been addressed yet by psychedelic researchers.

[ii]At least for anxiety in patients with terminal cancer and for patients with TRD. To our knowledge, this has not yet been assessed in the other populations that have been shown to benefit from psilocybin.

such as cognitive flexibility and mindfulness-related capacities like decentering.[35 36] Another hypothesis is that the therapeutic effects are mediated by making subjects more suggestible and open to therapeutic changes.[9] It is likely that psilocybin's mechanism of action is manifold and includes several of the above possibilities and others yet to be identified.

WHY ENHANCED CONSENT?

Some of psilocybin's effects are likely to be difficult for patients to appreciate beforehand, and in turn, require *enhanced consent* processes beyond those typical of many informed consent discussions. Importantly, the process we envision is enhanced relative to that of informed consent procedures used to prescribe other psychotropics. Nevertheless, it is based on established principles of informed consent.

There is a shared consensus among ethicists and legal scholars that providers are obligated to disclose the information that a reasonable patient would want to know about the treatment in question.[iii] [37 38] In general, the fundamental elements of disclosure are the nature of the procedure, the risks and potential benefits and what alternatives may be available.[38] While debate continues about the specificity regarding these elements in various contexts, there is consensus that the standards vary according to context and the intervention in question. For instance, standards for invasive surgery are higher than those for blood draw.[39]

Clinically, disclosure of the critical elements for most psychiatric interventions can be covered in a few minutes. For instance, disclosure for consent to use of selective serotonin reuptake inhibitors (SSRIs), such as escitalopram, can cover the common side effects, including gastrointestinal distress and sexual difficulties, and severe ones, such as serotonin syndrome. Similarly, for second generation antipsychotics, such disclosure can cover common side effects of weight gain, dizziness and orthostatic hypotension as well as more severe, but rare, side effects like dystonic reactions and neuroleptic malignant syndrome relatively quickly. After introducing these elements, the provider can then invite any questions and direct patients to informational handouts if the patient finds these helpful. Finally, while consent to research is more rigorously regulated and monitored than in medical practice, generally, the chief concern about these particular agents that is different in research will be about understanding the fact that a patient is enrolled in research and, for randomised trials, may not receive the agent under investigation. Thus, in keeping with significant efforts to simplify consent forms and discussion,[39 40] many consent interactions in psychotropic research can be relatively straightforward.

The rationale for such simplicity in informed consent for these psychotropics stems in large part from the fact that a reasonable person can be expected to care mostly about the most common and most severe effects. For SSRIs and antipsychotics, patients are unlikely to care about the details of mechanism and side effects on their personality—which, at least in the case of SSRIs for which there is more compelling data than for antipsychotics, are limited relative to those of psychedelics.[iv] Hence, relatively little attention is paid to complex scientific information about underlying pharmacological mechanisms or to personal preferences, values and deeper concerns of participants. This contrasts with the case of psilocybin, where talking about relieving depression, or even further, the general possibility of hallucination during the psychedelic experience and the risks of anxiety during it, may not make clear to patients the profound effects reviewed above, which may be critical to their decision-making about the intervention.

DISCLOSURE TOPICS IN ENHANCED CONSENT

More specifically, we believe that three components of the therapeutic process, mechanism and side effect profile of psilocybin will be novel and potentially unexpected for patients. These are shifts in values and personality, rare mental health side effects and the possible use of therapeutic touch during therapy. They thus require special attention in enhanced consent.

Shifts in values and personality

Two risks regarding change in values and personality are worth noting. First, some of the personality changes reviewed above may be unwelcome to subjects if their newfound values are antithetical to their former ones. For example, non-spiritual, agnostic or atheist patients may take the development of a newfound sense of spirituality or belief in God to be a loss if it is incongruent with their prior values or if it is disruptive to relationships with others. Similarly, religious patients who believe a mystical experience requires intensive spiritual work or a divine gift could be troubled if through treatment, come to see it reduced to a biochemical cause.

Second, if psychedelic experiences are truly ineffable, their intensity as well as the possibility of changes to personality may be difficult to convey in consent conversations. For example, before the experience, atheist patients might not appreciate that they too could have intense spiritual experiences. Instead, they might acknowledge that others have deep encounters *as if* connecting to God or 'deep' reality, but assume that they themselves would not take such encounters as *real*—even if therapeutically beneficial. Enhanced consent may increase the probability of patients' appreciating the possibility of personality change.

Mental health risks

The second component is that of rare mental health risks—particularly those of severe anxiety of the experience, psychosis, and trauma re-exposure. First, while 'transient anxiety' (frequently considered 'mild' or 'moderate') is described as one of the chief risk factors in the literature,[4] 39% of those surveyed about negative consequences of (mostly recreational) psilocybin use reported their worst 'trip' to be one of the five most challenging experiences of their life.[41] Thus, while such experiences are likely different from those in controlled settings,[41] we should take the possibility of severe anxiety seriously, and note that it could become more common with clinical psilocybin use outside of the tightly controlled experimental environment.

The second mental health risk is that of psychosis. Here, it is noteworthy that clinical trials have reported no episodes of psychosis in participants. This may be due to careful screening of patients to minimise risk of psychosis and substance use.[9] Yet, such screening may relax as psilocybin transitions to clinical psychiatry given that, as a rule, the fidelity of safety monitoring, treatment protocols and other standards is far higher in research practice than in clinical practice where oversight is often looser and time demands are often higher.

Some authors suggest that concerns about the negative, 'long-term' psychological effects of psychedelics—and in particular

[iii] Or in some jurisdictions what a reasonable provider would disclose.[37 38] We will emphasise the reasonable person standard as most bioethicists do, but everything we say below could be expressed in the language of the reasonable provider.

[iv] See the section 'Is psilocybin relevantly different?

of psychosis—are 'largely unfounded'.[20] They point to cross-sectional interviews that find no association between mental health symptoms, including psychotic symptoms, within the past year and lifetime psychedelic use.[42] However, the survey about negative consequences of psilocybin use noted above found 3 self-reports consistent with enduring psychosis after psilocybin usage.[41] Notably, this was a very small percentage of the 1993 individuals surveyed. Additionally, without further evidence, these self-reports may not be grounds to infer causation and may not be statistically significant.

Nevertheless, other considerations should give further pause to the conclusion that concern about psychosis is 'unfounded'. For one, a hallmark of substance-induced psychosis is that symptoms remit shortly after the event. Indeed, the *Diagnostic and Statistical Manual of Mental Disorders* takes the persistence of symptoms for greater than a month after cessation of the substance to be one of the paradigmatic examples of evidence that a primary psychotic disorder should be diagnosed despite active substance use.[v] [43] Hence, a lifetime history of use, complicated by substance-induced psychosis, would not necessarily correlate with recent symptoms—mitigating the implications of the otherwise reassuring cross-sectional interviews.

Another consideration that gives pause to the conclusion that the concern about psychosis is unfounded, there may be psychosis-related risk other than that of acutely inducing psychosis. Hallucinogen abuse is a risk factor for developing schizophrenia, and hallucinogen use by individuals with schizophrenia is a risk factor for violent behaviour.[vi] [44 45] Hence, while the risk of psychosis for any individual is likely low, it does appear sufficient for clinical attention, both for safety and for obtaining consent. Enhanced consent should call attention to these risks—though it should, of course, contain reassurance that in controlled settings the risk is exceptionally low.

The third mental health risk is that of trauma re-exposure. Subjects have noted that they relived traumatic experiences during the psychedelic experience or even experienced completely new, putative 'memories' of trauma.[4 29] Indeed, sometimes therapists cannot assess the accuracy of such new memories.[4] Clinicians will have to both inform subjects about such a possibility as well as be prepared to address it. The possibility of reliving traumatic experiences merits careful discussion in the informed consent process.

Therapeutic touch

Finally, psychedelic psychotherapists have expressed ethical concern about the bounds of therapeutic touch in psychedelic therapy, such as occurs in holding the patient's hand to offer support during a difficult experience. The use of such touch has long been controversial in psychotherapy—particularly in the psychodynamic context[46 47]—and surveys reveal variations in the ways and frequency with which it is employed.[48 49] Many psychedelic psychotherapists use therapeutic touch,[50] and so we must consider complexities related to patient consent to it.

Presumably, if therapists are to employ touch at all, they should do so only if it is therapeutic and requested by the patient.[50] Further, while there might be concerns about the possibility of exploitation of a vulnerable patient, these are mitigated in part by the fact that current protocols require therapists to work in pairs—ensuring the presence of a consultant and witness.

Nevertheless, challenges arise when patients change their minds about whether they would or would not like therapeutic touch during the psychedelic experience. Changes in preferences are particularly challenging because the psychedelic state may undermine patients' decision-making capacity. Moreover, decision-making capacity may be difficult to assess since it often involves a variety of questions about patient preferences and rationale that may be both impractical and counter-therapeutic to ask to a patient in the midst of anxiety that might warrant therapeutic touch during the psychedelic experience.[vii]

However, even if such assessment is impractical, ethical guidance can be offered. In particular, we imagine three scenarios that merit distinct considerations. In the first, a patient may consent to therapeutic touch during the consent process but later, when confronting anxiety during the psychedelic experience, reject it. In such a case, therapists must not touch a patient against their will; here, the duty to respect autonomy holds despite the fact that the psychedelic state may sometimes undermine the patient's decision-making capacity.

The second scenario occurs where a patient initially declines therapeutic touch but has become agitated and, further, is now a safety risk to themselves or others. In such a case, redirection, or even restraint, may be required. We do not anticipate this case arising frequently in psychedelic psychotherapy, but importantly, both the nature and justification of such intervention is different from that of therapeutic touch and should not be confused with it.

A third kind of scenario presents when patients initially decline therapeutic touch during the consent process but when experiencing distress in the psychedelic state, they change their mind and ask to be touched. In such cases, it may be ethically appropriate to provide the patient with therapeutic touch despite their initial declination and the fact that the patient may be technically incapacitated. Here therapists will have to exercise their judgment carefully, but ideally, in such cases, a second therapist should provide immediate consultation to assess the shift in the patient's decision and the appropriateness of such touch.

Additional research is necessary to determine the frequency with which patients change their preferences and how they feel about various policies and practices regarding touch. Using these findings, the psychedelic psychotherapy community should develop harmonized standards for therapeutic touch. In fact, the Multidisciplinary Association for Psychedelic Studies (MAPS)—a leader in psychedelic psychotherapy—has recently offered imporant guidance on these issues.[50] MAPS suggests identifying 'simple and specific words and gestures' the patient may use to communicate their preferences during the experience. However, further development of such standards will be needed as research progresses, and in particular, guidance should be developed for how to respond to cases where patients change their minds about therapeutic touch. Legal and ethics scholars should help in developing standards—both in providing expertise about similar cases from other medical specialties and in assessing how the law might respond to standards under consideration.

[v] P. 110. Hence, while the possibility of psychedelic treatment triggering hallucinogen persisting perception disorder was initially of significant concern at the dawn of the psychedelic renaissance,[9] and while there may be reason to think such concern was overstated,[42] this does not speak to the concern of a substance-induced psychotic state which is a distinct diagnostic entity.

[vi] Though interpretation of such results for work with classic psychedelics must be taken with caution because hallucinogens are a diverse class of drugs not limited to classic psychedelics.

[vii] On the predominant view, these include the abilities to express a stable preference, to understand the information relevant to the decision, to appreciate the impact of the decision and to rationally manipulate the information in making a decision (at least to some degree).[65]

Table 2 Suggested disclosure information and questions for consent to psilocybin

Information about the experience	'You may think you are communicating with higher powers or understanding 'deeper' realities. This happens to people who have spiritual and religious beliefs, but also to those who do not have such beliefs. Those who have experienced this often find it difficult to convey to others exactly what they experienced. Hence, we cannot tell you exactly what this is like, and you may have trouble understanding it before you experience it yourself.'
	'You may feel profound connections that would have seemed odd to you prior to this experience. These may include connections with various people (perhaps all of humanity) as well as animals and nature generally.'
	'You may feel a sense that you have lost yourself, that everything is somehow connected, or that all is one.'
Information about potential long-term changes	'You may become more open to new experiences and different points of view.'
	'You may become more spiritual—whether or not you currently consider yourself spiritual.'
	'You may feel a deeper connection with nature.'
	'You may feel a greater sense of extroversion and openness to new experiences and ideas.'
	'These changes may lead you or your family to perceive you as different in various ways.'
Information about mechanism	'The benefits of this intervention may be related to or depend on these effects of the experience and these changes to your personality. We have found that encouraging participants to embrace the experience is important to achieving the benefits. In fact, trying to resist aspects of the experience can lead to more anxiety provoking and less beneficial outcomes.'
	'The benefits may also be related to the power of suggestion that the drug enables. For instance, patients with cancer have seen decreases in their depression with the experience. This might be, in part, because it helps them to accept the idea that their cancer lacks power over their mood and meaning in life.'
Therapeutic touch	'We can use our clinical discretion to support you during intense moments in the psychedelic experience, for instance by holding your hand if you become distressed. However, we would never do this unless you wished. Would you like us to? If so, we should talk about how to communicate about this during the experience.'
Questions for subjects' reflection	'Would any of these changes be difficult for you?'
	'Do you have any further questions about this experience, its risks, or its benefits?'

Having now reviewed several features that are critical to discussion in enhanced consent, we offer discussion prompts for the enhanced consent process in table 2.

ENHANCED CONSENT AND CURRENT PRACTICE

Do current research practices meet the demands of enhanced consent? Perhaps so—particularly during the sessions designed to prepare research participants for psychedelic psychotherapy. The state of the art for such sessions was described early in the psychedelic renaissance through a set of safety guidelines for psychedelic research by Johnson *et al*.[9] Regarding informed consent, those guidelines note that the psychedelic experience may be difficult for psychedelic-naïve participants to understand and that, hence, more time may be required to discuss such effects than would otherwise be the case. They also emphasise that participants should be told about a number of the possible effects of psilocybin use, including many that we discuss above and particularly psychedelic-induced disorders in the consent process.

Perhaps more interestingly, they then detail preparatory sessions, which many might take as a separate step from the informed consent process. These sessions are not only designed to introduce subjects to logistics of treatment sessions and build a therapeutic relationship with participants, but also to provide 'a detailed discussion of the possible range of [psychedelic] experiences' as well as guidance on how to address challenging experiences. However, we believe that such discussions should be considered not merely part of the preparation for therapy. Rather we would urge that such sessions also be thought of as part of informed consent. We would urge that such sessions be thought of as part of the extended process of consent, offering recurrent opportunity to improve subject understanding and achieve enhanced consent.

Nevertheless, we know of no detailed reviews that have surveyed the exact protocols of preparatory sessions across different psychedelic studies or any describing details of informed consent processes across various psychedelic studies. Hence, we cannot assess the degree to which our standards are met in current research practice with certainty, but we hope, that in providing them, we can aid in their being regularly realised in both research and future practice.

IS PSILOCYBIN RELEVANTLY DIFFERENT?

The chief concern about our argument may be skepticism about our claim that psilocybin is different from standard psychotropics, like SSRIs. Indeed, psychedelics are not the first psychotropic to raise concerns about changes to patients' personalities. Similar concerns were raised about SSRIs over 20 years ago.[51] SSRIs appear to decrease neuroticism and increase conscientiousness.[26 52–54] Similarly, psychotherapy in various forms, including CBT, supportive, psychodynamic, hospital-based and mixed therapy modalities, appears to change personality as well—perhaps more than conventional antidepressants.[55] Thus, some might ask: 'Is psilocybin really different?'—at least regarding one of the most significant novel risks—that of personality change. The answer is yes.

There are critical differences between psilocybin and conventional psychiatric treatments. First, while data are preliminary, the personality changes effected by psilocybin are different in both kind and degree from those of traditional psychiatric intervention. While they share alterations in neuroticism and conscientiousness with conventional antidepressants, evidence suggests that psilocybin induces significant changes in extraversion and openness compared with conventional antidepressants.[viii 26] As noted above, the effect on openness may be critical to the mechanism of psilocybin; hence, this difference in effect size is crucial.

Second, patients may incorporate evidence from their experience of conventional psychopharmacological and psychotherapeutic interventions to their decision-making about continuing with such interventions. Having experienced part of

[viii]The precise measure is rough because it relies on changes measured in different trials.[26] To our knowledge, comparison of psychedelics to particular psychotherapeutic modalities has not been estimated.

a therapeutic process, they can decide whether to continue it. This allows for longitudinal processes of revisiting the disclosure process to informed consent. In contrast, they may lack the time to do so with psychedelic interventions because the psychedelics' effects appear to happen quickly with single doses. Therefore, the ethical importance of patients' understanding information about personality changes before engaging in psilocybin treatment may be much greater than that of their understanding of such change in conventional therapy, which they may terminate at any time.

Finally, not all of the personality changes elicited by psilocybin seem to be explained by changes that are well-measured by the Five-Factor Model. Many of psilocybin's effects reviewed in Section I, such as its ability to induce new ineffable realisations of the deep connections between all things or of truth or of God, appear to affect personality without obviously affecting any of the five factors. These changes are at least as ethically salient as changes to those factors. Such changes are not typical of conventional antidepressants. Moreover, they are not paradigmatic features of conventional psychotherapy as such—though undoubtedly existential subjects may sometimes be a feature of such therapy. Even when this occurs in conventional therapy, the process through which it happens is generally not ineffable, mystical or rapid, so subjects may have more control over whether and how they wish to accept such changes as part of themselves.

SUGGESTIBILITY AND CAPACITY TO CONSENT

Two other objections must be addressed. First, one might object that enhanced consent might limit psilocybin's power to induce suggestibility, potentially affecting its therapeutic effects given that this may be part of its mechanism.[5 9] Perhaps hearing about personality changes or the potential role of suggestibility in psilocybin's mechanism may render subjects less open to suggestion, reducing effect size and therapeutic power. Further, this might raise research concerns about difficulties in controlling for this disclosure-related effect.[17]

Yet, given the discussion above, failure to discuss this may be withholding material information from patients. Hence, the standard requirement of informed consent to discuss information that can be expected to be material to decision-making[37] (unless waived by the patient) implies one ought not withhold this information. Additionally, the considerations raised by this objection point to further reasons for enhanced consent. First, patients may not be as interested in a form of pharmacology that makes them more suggestible to certain beliefs that they would not otherwise endorse. Second, if new trials with enhanced consent result in a smaller effect size for psilocybin, we would gain valuable knowledge about suggestibility and psilocybin's mechanism. While such a finding might limit some of the current enthusiasm about psilocybin, it might also suggest a mechanism that other novel therapies could be developed to target.

The final objection charges that patients cannot consent to psilocybin—even under the conditions of enhanced consent—if psilocybin-assisted psychotherapy involves experiences that are inarticulable. When we attempt to assess the subjective value of some event, we often do so by imagining what it—and its results—would be like to experience.[56] Unfortunately, if the event or results are not possible to appreciate before having the experience, we lack the information critical to this process. Indeed, some bioethicists have claimed that similar imaginative exercises are necessary for one to have a rational desire—one that is an expression of one's autonomy.[57] In turn, if psilocybin induces truly ineffable experience (or changes that are too difficult to appreciate), one might question whether one can give informed consent to psilocybin-assisted psychotherapy.

Yet, we doubt that being unable to fully imagine the experience or outcomes undermines one's ability to give consent.[ix] After all, we regularly accept consent to various activities that cannot be fully imagined—including beginning new relationships, getting married, starting a job and moving. Likewise, we take consent to traditional psychotherapy as authoritative despite effects on personality and worldview that subjects cannot fully appreciate before therapy.

THE ETHICS OF GOING MAINSTREAM

To conclude, we review the cautionary history of previous (ultimately unfounded) concerns about personality-altering therapies. This should remind us that the data on psilocybin are still largely preliminary. We then turn to four issues beyond those of consent that are critical as psilocybin transitions to mainstream psychiatry.

There is a long history of concerns about personality-changing interventions beyond the concerns about SSRIs' effects on personality noted above. Many lay people have raised concerns about such changes from organ transplants, particularly heart transplants—though many such concerns rely on implausible beliefs about the physiological process through which the organ itself might induce such change.[58] Perhaps more plausibly, ethicists have historically been concerned about personality change from deep brain stimulation. Yet, systematic review has found that evidence of personality change from deep brain stimulation is found only in an extremely small percentage of studies and that the studies with such findings were all uncontrolled. Moreover, several of these studies noted potentially better explanations for the observed behavioural changes than changes to personality.[59] Additionally, ethicists have worried that face transplants were ethically problematic given the importance of facial features in social identity. Yet, when transplants proved successful without evidence of such problems, commentary became much more favourable.[60] Many now believe that those initial concerns about face transplantation rested on little more than poorly founded speculation.[61]

This history reminds us of the importance of caution in drawing conclusions from initial research. In the case of psilocybin, we must remember that the initial data reviewed above on psilocybin's effects generally—and on personality in particular—is still preliminary. Thus, we must emphasise that more research is required and that ethical conclusions must be tentative. Nevertheless, we believe the above arguments support enhanced consent for psilocybin—at least precautionarily until further evidence suggests otherwise.

Similar ethical caution will be critical as the use of psilocybin transitions from a limited research setting to psychiatric practice; in particular, four issues that will be crucial. First, if we are right that psilocybin induces personality changes that are not well-accounted for on the Five-Factor Model, further research is needed to understand this personality change. Indeed, we may even need new instruments to assess how participants understand changes to personality—given that the Five-Factor Model (the dominant model of personality in psychology) does not

[ix]Imagining such experience is obviously a matter of degree, and whatever it is for the psychedelic experience to be ineffable, it is certainly *somewhat* imaginable.

appear to do so.[x] Given the importance of personality in mental health, a model that accommodates these other types of personality change may offer contributions far beyond the realm of psychedelic psychiatry.

Second, psilocybin is like other novel therapeutic modalities in that ethical challenges arise because knowledge of mechanisms, safety and further benefits is limited and norms about standard practice outside of the research context have yet to emerge. Thus, it is important to develop careful policy safeguards for the most obvious risks, including anxiety, psychosis and trauma exposure. In particular, these risks could be exacerbated if clinical psilocybin use evolves as ketamine use did, where robust (or even overzealous) enthusiasm emerged. If so, clinics could begin to use non-standard dosing or minimise safeguards.[62 63] Others have proposed a Risk Evaluation and Mitigation Strategies through the Food and Drug Administration;[64] this could be one way of maintaining safety (potentially combinable with others) as psilocybin transitions to clinical use.

Third, it is standard practice for intense psychotherapy to be conducted in the research setting with psychedelics including psilocybin. While no trials have been conducted to demonstrate that such psychotherapy is necessary (or to assess how much is necessary) for benefit or safety, anecdotally, experienced therapists believe it is critical. Yet, therapy can be expensive and time-consuming; hence, eliminating a requirement for psychotherapy may be a tempting means of increasing access. Undoubtedly, research should begin to address the question of how much—if any—therapy is necessary. Yet, in the meantime, given that experienced therapists believe it is critical, the precautionary principle would suggest that clinical psilocybin therapy should always involve integration therapy (or some therapeutic equivalent) to address the experiences that arise while using psilocybin. Such therapy may help in monitoring and addressing both psychosis and trauma exposure.

Finally, it must be emphasised that participants appear to have profoundly positive feelings about the experience. Hence, the risk-benefit analysis of psychedelic intervention seems favourable for those who are screened as having low-risk for psychosis—even more so when we note the potentially profound effects on illness. Despite the ethical considerations presented here, if the initial benefits of psilocybin can be replicated in Phase III trials, there will be an ethical imperative to proceed with a transition of psilocybin to mainstream psychiatry.

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[x]Or perhaps we should turn to less commonly used scales that better capture the relevant dimensions. One study found that regular uses of ayahuasca scored higher than controls on the self-transcendence component of the Temperament and Character Inventory—an inventory that measures novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness and self-transcendence.[66 67] We thank a reviewer for this journal for pointing us to this study.

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