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RESPONSES AND DIALOGUE

Psychedelics, Meaningfulness, and the "Proper Scope" of Medicine: Continuing the Conversation

Katherine Cheung[1], Kyle Patch[2], Brian D. Earp[3] and David B. Yaden[4]

[1]Department of Bioethics, New York University, New York, NY, USA
[2]Department of Bioethics, National Institutes of Health Clinical Center, Bethesda, MD, USA
[3]Uehiro Centre for Practical Ethics, University of Oxford, Oxford, UK
[4]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
Corresponding author: David B. Yaden; Email: dyaden1@jhmi.edu

Introduction

Psychedelics such as psilocybin reliably produce significantly altered states of consciousness with a variety of subjectively experienced effects. These include certain changes to perception, cognition, and affect,[1] which we refer to here as the acute subjective effects of psychedelics. In recent years, psychedelics such as psilocybin have also shown considerable promise as therapeutic agents when combined with talk therapy, for example, in the treatment of major depression or substance use disorder.[2] However, it is currently unclear whether the aforementioned acute subjective effects are necessary to bring about the observed therapeutic effects of psilocybin and other psychedelics. This uncertainty has sparked a lively—though still largely hypothetical—debate on whether psychedelics *without* subjective effects ("nonsubjective psychedelics" or "non-hallucinogenic psychedelics") could still have the same therapeutic impact, or whether the acute subjective effects are in fact necessary for this impact to be fully realized.[3,4,5]

Although nonsubjective psychedelics currently do not exist, interest in developing such compounds from private companies and other stakeholders is currently growing. Within this context, a pressing bioethical question has arisen—namely, *if* so-called subjective and nonsubjective psychedelics could be shown to have the same therapeutic impact, which we stress is *not* an empirical guarantee at this point and may not be possible,[6] should subjective psychedelics still remain the default treatment offered? Or might there be strong ethical reasons to switch to nonsubjective psychedelics as the standard of care, thus relegating subjective psychedelics to a secondary position or "backup" status?

A previous article by David Yaden, Brian Earp, and Rolland Griffiths[7] (2022) argued for "subjective psychedelics" (i.e., current psychedelics) to be offered as the default, even under the above-described hypothetical circumstances in which therapeutically effective "nonsubjective psychedelics" were created. Their argument was grounded in several lines of reasoning. First, they noted that respect for patient autonomy requires that patients be allowed, where feasible, to choose and to pursue those ends which they themselves value, especially in the context of shared medical decisionmaking. Accordingly, Yaden, Earp, and Griffiths argued that patients who would prefer subjective psychedelics—for example, because they place a high value on the conscious states induced by such substances, over and above specific treatment-oriented outcomes—should not face unnecessary hurdles to selecting this option (e.g., by first having to try nonsubjective psychedelics), assuming it could be made available in a cost-effective manner alongside any alternative options that might be developed.[8]

Second, and with the same caveat, they argued that physicians may have a positive obligation grounded in the principle of beneficence to offer subjective psychedelics as a default. This is because, again, in addition to treating certain recognized medical conditions, such psychedelics have been shown to carry a significant likelihood of fostering "one of the most positive and meaningful experiences of a patient's life without undue risk."[9] On this view, the fact that such a benefit may seem *conceptually* distinguishable from more paradigmatically "medical" outcomes (e.g., the relief of suffering caused by an

aberrant biological or psychological condition, where the relief is due to the correction of the condition) does not make it *practically* or *normatively* distinguishable. Instead, all potential benefits of a given treatment option must be factored into doctors' medical decisionmaking, if they are to fully realize the ethical principle of beneficence. In a response piece, Kurt Rasmussen and David Olson take a contrary position.[10] They argue that the risks of using subjective psychedelics (e.g., the potential for aversive experiences), in addition to possible future differences in accessibility and affordability (discussed below), speak in favor of switching to nonsubjective psychedelics as the default. Moreover, they suggest that the meaningful experience often afforded by subjective psychedelics may be outside the scope of medicine, as "people do not need to be seeking treatment for a disease to rate a psychedelic experience as being among the most meaningful experiences of their life."[11] They conclude that meaningfulness as such is not relevant to the current debate. Andrew Peterson and Dominic Sisti similarly disagree with Yaden, Earp, and Griffiths (2022), arguing that physicians' professional and ethical obligations "do not require them to provide nonmedically relevant experiences on the grounds that they could be meaningful or existentially transformative."[12] Only considerations of treatment effectiveness, they argue, rather than what they characterize as "extra-medical" values, should inform decisions about the standard of care.

Before responding to the above arguments, we must express our recognition and appreciation of the value of researching nonsubjective psychedelics. This nascent line of inquiry will further clarify the role of underlying neurobiological mechanisms and could potentially lead to new treatment options for patients for whom subjective psychedelics are in fact contraindicated (for example, those at a high risk of psychosis, or with a family background of schizophrenia). We would even approve of their being offered alongside subjective psychedelics, that is, on equal footing, as an option for those who might simply prefer them for whatever reason (i.e., even if subjective psychedelics were not specifically contraindicated in their case). Again, this would be on grounds of respect for autonomy. What we would oppose is the removal of subjective psychedelics from the set of first-line options from which medically eligible patients could choose.

That being said, *while reiterating the largely hypothetical nature of this debate, as the therapeutic efficacy of nonsubjective psychedelics is at present unknown and remains unpredictable*, we will now respond in greater detail to the various points raised by our interlocutors.

Risk/Benefit Ratio, Financial Considerations

Given the preliminary nature of the debate as just described, it may seem premature to argue that future/potential nonsubjective psychedelics may have a higher or lower risk/benefit ratio compared to current/actual subjective psychedelics. However, we will offer some tentative observations and reflections that are likely to be relevant for assessing future developments in this area.

Although the use of nonsubjective psychedelics could hypothetically remove some of the risks that accompany psychedelic-induced subjective experiences, novel risks may also emerge from the use of nonsubjective ones. One potential risk could stem from individuals' being in a highly neuroplastic state without concomitant changes to conscious experience alerting them to this fact, or without the same level of therapeutic support (if this ends up being the modality through which nonsubjective psychedelics are offered, e.g., on cost-saving grounds). This could lead them to unwittingly put themselves in a vulnerable situation—one in which their more plastic brain is being subtly subjected to various influences, but without as a clear a "container" or conscious stimulus to attend to them or try to process them adaptively. When evaluating risks and benefits, it is important to note that subjective psychedelics do carry risks, and aversive experiences with persisting negative effects can and do occur.[13,14] However, the actual likelihood, persistence, and magnitude of these risks must be weighed against the same in relation to subjective psychedelics' known potential benefits. Moreover, these risks must be placed in context with other recreational psychoactive substances and non-recreational pharmacotherapies to understand their practical significance. In this context, psychedelics[15] are less harmful and more physiologically safe than many other substances such as alcohol. They also have an extremely low potential for addiction as demonstrated in animal models, with fatal overdose events being practically unheard of.[16] That being said, unpleasant experiences, unwanted psychological changes, and heightened vulnerabilities or behaviors that put one at risk of physical or emotional harm may sometimes

occur while under the influence of subjective psychedelics (although this can be mitigated with due attention to set and setting).[17]

But then, some of these risks may also pertain to the use of nonsubjective psychedelics. Although, by stipulation, these risks would not include immediate or acute unpleasant experiences, longer-term unwanted psychological changes and/or increased emotional or other vulnerabilities might still plausibly occur (e.g., as a result of biological changes—or biology-psychology-environment interactions—taking place under conditions of increased neuroplasticity, albeit, again, without the concomitant acute subjective awareness of being in an abnormal state). There is no way, at this point, to be certain that these risks would not outweigh those of current subjective psychedelics.

It is also uncertain as to whether nonsubjective psychedelics would be more financially accessible than subjective ones. The development of these compounds could arguably entail higher costs for patients as pharmaceutical companies seek to recoup their investment in research and development and, as Peterson and Sisti write, "manufacturing novel compounds would allow drug companies to profit from substances that have long been used in indigenous communities."[18] Further, while the need for the adjunctive therapeutic ensemble in the case of subjective psychedelics might entail higher short-term costs, their noted ability to produce significant symptom reduction in just one, or a few, administrations could result in lower *net* spending compared to nonsubjective psychedelics insofar as the latter would be prescribed for ongoing use.[19] Still, price transparency initiatives and fair pricing models will be imperative for both modalities.

Inclusion of Vulnerable Persons

In advocating for nonsubjective psychedelics as the default treatment option, Rasmussen and Olson argue that these substances might benefit populations excluded from treatment by subjective psychedelics. Indeed, most psychedelic trials exclude individuals due to various risk factors, such as a personal/familial history of serious mental illness (e.g., psychotic disorders), or suicidal ideation or behavior. Given that these populations might stand to benefit the most from developments in psychedelic research, if associated risks could be appropriately mitigated, greater inclusion in treatment is a significant priority for the field.

Accordingly, Rasmussen and Olson argue that "we have an ethical obligation to ensure that patients in need of psychoplastogenic medicines have access to them."[20] Rasmussen and Olson further suggest that arguments in favor of a positive obligation to make subjective psychedelics the default treatment option due to their distinctive potential benefits (e.g., increased sense of well-being, meaningful or transformative experience) might not hold if these benefits are not equitably distributed and "only available to a select few."[21]

First, in response, we note that "the select few" likely does not accurately describe the set of persons who, based on current evidence, would stand to benefit from default access to subjective psychedelics as the standard of care. On the contrary, it is the limited, specific set of persons who will have unresolvable contraindications to their use who would require an alternative treatment modality, while all others would remain potential candidates to be beneficiaries. Nevertheless, this might still seem to raise the question of whether inequitable benefits, as Rasmussen and Olson call them, should be made unavailable to everyone (i.e., all groups) simply because they cannot be made available to some groups. But even more fundamentally, it is an open question whether such benefits are in fact truly inequitable (that is, unjustly unequally available) as opposed to simply unequal (but not unjustly so).

Virtually all would agree that particular groups of people should not be singled out for exclusion from an otherwise promising treatment modality based on medically or morally irrelevant features (e.g., gender, race). However, when differences in health options and outcomes are not the result of unjust discrimination or unfair disadvantage, it is less clear that an objectionable inequity is at play. Take, for example, Herceptin, a breast cancer drug that works most effectively for people who express the HER2 gene. In order to determine eligibility for Herceptin, patients must undergo genetic tests for the

aforementioned gene.[22] Those who do not express the gene may not be eligible for Herceptin treatment, but this would not be due to unjust discrimination against them; rather, this would be due to a relatively unfavorable risk–benefit profile in their case. Another relevant example might be fluoxetine therapy (commonly known as Prozac). Due to its mechanism, it is not recommended for those who have epilepsy or are prone to seizures.[23] But just because persons with those conditions may not be good candidates for the specific treatment in question, this does not mean that it should be withheld from everyone. Rather, alternative treatments should be researched and made available for people in those particular high-risk subgroups.

In short, *equal* access to certain medical interventions is not *a priori* equitable. People have different needs and vulnerabilities; one size does not fit all. Instead, factors such as genetics, serious mental health risks, or (other) potential contraindications may require differential access based on several considerations. These will include the best available evidence regarding the risks and potential benefits of the treatment as applied to specific populations; the unique situation, needs, values, and preferences of particular patients (e.g., regarding personal tolerance or acceptance of different types or degrees of risk in relation to potential benefits); and sound clinical judgment.

Finally, in the case of subjective psychedelics, if "equal" (rather than truly equitable) access for everyone entails no (or highly constrained) access for anyone, the overall or aggregate cost to human well-being could be considerable. Such an outcome (i.e., lost opportunities for experienced meaningfulness, adaptive positive mood, feelings of peace, joy, tranquility, and so on)[24] would seem highly regrettable. As we see it, a commitment to equity involves providing access and treatment based on need and patient-specific values, risks, and benefits. Providing subjective psychedelics as the default would not violate this commitment since patients who could benefit would be able to do so, while patients with decisive contraindications would still have the option (in this hypothetical scenario) to choose nonsubjective psychedelics as an alternative. To that end, we agree with Rasmussen and Olson that there are strong moral, as well as scientific and clinical, reasons to work toward researching and developing nonsubjective psychedelics.

Meaningfulness / "Nonmedical" Benefits

A primary argument in favor of subjective psychedelics as standard of care is that they have a significant potential of inducing, in an appropriately supportive context, an experience that is highly conducive to patient well-being while also being felt or interpreted as profoundly meaningful. On some views, well-being is partly constituted by a sense of meaningfulness in one's life; on other views, meaningfulness is intrinsically valuable, even apart from well-being—while also often (but not necessarily always) increasing well-being instrumentally or as "side-effect." Either way, it is noteworthy that a majority of participants across a number of clinical trials rate the psychedelic experience as being one of the most meaningful in their lives, 6–14 months after administration.[25]

Although the acute subjective effects of psychedelics can be challenging to participants (e.g., sometimes causing anxiety or panic), a survey of recreational users found that participants did not view the experience of fear or anxiety as rendering the psychedelic experience all-things-considered undesirable or contrary to well-being. Instead, many (though not all) interpreted these emotions as being meaningful, and hence valuable, in themselves.[26]

However, both Sisti and Peterson and Rasmussen and Olson argue against the inclusion of this line of reasoning in their respective papers, for similar reasons. Sisti and Peterson write that neither meaningfulness nor positive self-transformation fall under the purview of medicine and are thus nonmedically relevant. They suggest it would be inappropriate, therefore, to base a medical decision on what is essentially an "extra-medical" benefit. Similarly, Rasmussen and Olson argue that the perceived meaningfulness of an experience is not within the scope of medicine.

However, in addition to our earlier point about the practical and normative inseparability of "medical" and "nonmedical" benefits in the case of subjective psychedelics, we would note that meaningfulness does seem to be an element that is taken into consideration in various mainstream

areas of medicine and/or medical decisionmaking—and seemingly, appropriately so. When making end-of-life decisions, for example, patients frequently balance competing considerations of whether to be more aware (and thus able to process the meaning of their experiences) but in more pain, or to have less pain but be under heavier sedation, thus minimizing or precluding any meaningful experience.[27] In making these decisions, physicians often provide medical guidance with the goal of helping patients attain not only a reduction in pain or suffering (i.e., paradigmatically medical aims) but also a personally meaningful end of life. Thus, meaningfulness is not only an implicit value taken into consideration by individuals and physicians in certain common medical contexts,[28] but also often an explicitly stated goal in clinical care.

Nonetheless, whether meaningfulness (considered as a type of benefit) *ought* to be considered medically relevant likely depends on one's conception of "benefit" in relation to the proper scope of medicine (which is likewise a matter of disagreement).[29] Let us suppose that by "benefit" we mean a benefit to patient well-being. According to some views,[30] a patient's well-being can be understood in both subjectivist and objectivist terms. Subjective well-being is determined in part by the patient's own, potentially peculiar, preferences, values, and desires, while objective well-being is determined by a set of goods that are thought to be universally valuable, even if a patient does not recognize this fact (or personally value the goods in question). In a medical context, then, it may sometimes be necessary to ask, as Johan Bester has put it, "Should physicians be responding to subjective wellbeing [i.e., preferences and desires] or respond to objective patient needs?"[31]

The answer, in turn, depends on one's view of medicine. On a constricted view, according to which the proper aims of medicine consist solely of universally recognized, "objective" goods—like the treatment or prevention of suffering due to certain aberrant psychological or biological conditions (i.e., diseases or disorders)—it is plausible that the felt meaningfulness of a subjective psychedelic experience would not count as a "medically relevant" benefit. On a broader view, however, according to which medicine appropriately aims at health in line with the WHO definition—namely, "a state of complete physical, mental and social well-being [potentially including subjectivist elements] and not merely the absence of disease or infirmity"[32]—meaningfulness might in fact count as a "medically relevant" benefit, insofar as a patient prefers or desires it. This additionally aligns with the principle of autonomy and allows patients to choose what is of value to them.

Finding Areas of Consensus

Although evidence has not yet established whether nonsubjective or subjective psychedelics are equally effective, consensus between both camps can be found in many areas. Namely, it is universally agreed that the health and safety of the individual should take precedence and that the autonomy of individuals and their ability to choose should be preserved and prioritized. The challenge then remains to build a framework for the use of psychedelics upon these elements in combination with addressing considerations from both camps. If both are found to be equally effective, would a framework offering subjective psychedelics as the default with nonsubjective psychedelics offered to patients with contraindications or by personal choice be ethically warranted?

Rasmussen and Olson write that even if subjective psychedelics prove to be safe and effective, physicians should not have a duty to promote them to those with "strong personal, moral, ethical, or religious objections to the use of hallucinogenic drugs."[33] Importantly, a framework that emphasizes the autonomy of the individual would address situations such as these, by freely allowing patients with strong objections to choose nonsubjective psychedelics. As we assume both to be equally effective, physicians should not promote subjective psychedelics to those with strong personal objections, but instead describe the risks and benefits of both.

Similarly, inclusivity in the use of psychedelics is an element that can be addressed in the design of a suitable framework. Rasmussen and Olson, rightly, write that we have an ethical obligation to ensure access to psychedelics and broaden access if we are able to.[34] However, ensuring access to psychedelics should not be at the cost of those looking to access subjective psychedelics. If assuming equal

effectiveness, offering nonsubjective psychedelics as the default option may result in limited access to subjective psychedelics, as if an effective nonsubjective psychedelic is offered first, there may be no reason to try subjective psychedelics. However, it may be reasonable to assume that a sizeable percentage of individuals would like to benefit from the increased well-being and meaningful experience afforded by subjective psychedelics. A framework that offers subjective psychedelics as a default would permit individuals who wish to do so, to benefit from subjective psychedelics, while also letting patients with contraindications or personal objections benefit from nonsubjective ones. This framework maintains inclusivity as a value but to the detriment of neither group.

Conclusion

Overarchingly, there may still be reasons to offer subjective psychedelics as the default treatment, even after taking into account considerations of equity and risk/benefit profiles. Importantly, a framework with subjective psychedelics as the default allows patients to access benefits of value to them while preserving options for patients with contraindications. However, it is important to reiterate that nonsubjective psychedelics have not yet been created, and that the assumption of identical therapeutic effectiveness is simply being stipulated for the sake of this commentary. Further research will help elucidate whether this is true.

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