Cambridge Quarterly of Healthcare Ethics (2022), 31: 4, 477–481
doi:10.1017/S096318012200010X

CAMBRIDGE UNIVERSITY PRESS

COMMENTARY

Psychedelics as Standard of Care? Many Questions Remain

Kurt Rasmussen[1]* and David E. Olson[1,2,3,4]*

[1]Delix Therapeutics, Inc., Concord, Massachusetts 01742, USA
[2]Department of Chemistry, University of California, Davis, Davis, California 95616, USA
[3]Department of Biochemistry & Molecular Medicine, School of Medicine, University of California, Davis, Sacramento, California 95817, USA
[4]Center for Neuroscience, University of California, Davis, Davis, California 95618, USA
*Corresponding authors. Email: kurt@delixtherapeutics.com; deolson@ucdavis.edu

Psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and 5-methoxy-*N,N*-dimethyltrptamine (5-MeO-DMT) have emerged in recent years as promising therapeutics for a wide range of brain disorders, including but not limited to, depression, anxiety disorders, and substance use disorders.[1] These compounds have the unique ability to produce long-lasting therapeutic effects after a single administration,[2] though it is currently unclear if these sustained effects are the result of psychedelic-induced subjective experiences or the ability of psychedelics to promote cortical neuron growth and plasticity.[3,4] In fact, this question has been the subject of intense debate[5,6] as several nonhallucinogenic analogs of psychedelics have been reported recently.[7,8,9,10] David Yaden, Bryan Earp, and Roland Griffiths refer to these compounds as nonsubjective psychedelics,[11] but we prefer the term "nonhallucinogenic psychoplastogens,"[12] as it emphasizes the ability of these compounds to promote cortical neuron growth without inducing hallucinations.

Their rapid onset and sustained effects make psychoplastogens unique compared to traditional antidepressants such as selective serotonin reuptake inhibitors (SSRIs). Psychoplastogens have the potential to address major issues associated with SSRIs and related medicines including a delayed therapeutic response and limited efficacy.[13] Assuming that large phase 3 clinical trials replicate the preclinical and early clinical efficacy demonstrated by psychoplastogens, an important question will remain. Should hallucinogenic or nonhallucinogenic psychoplastogens be the preferred method of treatment? Yaden, Earp, and Griffiths contend that the subjective experiences induced by psychedelics will give patients a more positive experience, and thus, these compounds should be the default treatment option for most patients.[14] In their view, nonhallucinogenic psychoplastogens should be reserved for scientific research and for treating patient populations for whom psychedelics are contraindicated.[10] We believe that the field's understanding of the clinical effects of hallucinogenic and nonhallucinogenic psychoplastogens is too nascent to declare which option should be the standard of care, and moreover, the standard of care is likely to vary for different indications. However, assuming that hallucinogenic and nonhallucinogenic psychoplastogens produce comparable levels of efficacy, there will be ethical considerations for the field to consider. As Yaden, Earp, and Griffiths emphasize the importance of considering both negative and positive morality when making decisions about healthcare,[15] we will also use these concepts to frame our arguments.

Negative morality instructs us to "do no harm," a phrase that is embedded within the Hippocratic Oath. Although it seems that psychedelics can be administered safely to many patients under the care of a trained healthcare professional in a well-controlled environment, the true risks associated with these substances are not fully understood. For example, recent evidence suggests that the risk of adverse effects is significantly greater when psychedelics are administered in a nonmedical setting. After surveying nearly 2,000 individuals, Griffiths and coworkers found that 11% of psychedelic users put themselves or others in danger of physical harm during their most psychologically difficult or challenging psychedelic experience.[16] Moreover, nearly 8% of these individuals reported sustained negative psychological symptoms resulting from the experience that lasted for longer than 1 year and required additional medical attention.[13]

Two recent large clinical trials assessing the effects of psilocybin on depression excluded ~95% of potential participants due to various risk factors including a personal or family history of a psychotic illness.[17,18] For comparison, only ~25% of patients were excluded from similar sized trials involving the nonhallucinogenic antidepressant vortioxetine.[19,20] Neuropsychiatric diseases are highly heritable, characterized by overlapping genetics, and often comorbid, which raises questions regarding how effectively patients can be screened to prevent harm in a real-world context outside the confines of a clinical trial.

In addition to people with a personal or family history of psychotic disorders, there are additional patient populations for which hallucinogenic psychoplastogens may be contraindicated. For example, psychedelics should likely be contraindicated for patients with dementia despite the fact that many of these patients present with comorbid depression and/or anxiety phenotypes. Dementia is a symptom of many brain disorders including Alzheimer's disease, Parkinson's disease, frontotemporal dementia, vascular dementia, and Lewy body dementia, among others, and it reduces a patient's capacity for thinking and reasoning. For patients with even mild dementia, it may not be possible to establish the trust and rapport necessary for a therapeutic psychedelic experience, and patients with dementia may exhibit strong negative reactions to hallucinations. In fact, Griffiths and coworkers have demonstrated that psychedelics can induce strong feelings of fear in over 30% of healthy volunteers,[21,22] a number that could be higher in elderly patients with even mild dementia. Further, evoking strong feelings of fear may trigger panic attacks in vulnerable patients, suggesting that psychedelics may also be contraindicated for patients with panic disorder and other types of anxiety.

The risk/benefit ratio is an important factor for determining the standard of care for different patient populations. More research is needed to uncover the benefits and safety issues associated with hallucinogenic and nonhallucinogenic psychoplastogens in different patient populations. As an example, Griffiths and coworkers recently reported that patients with bipolar disorder who are using lithium may experience an increased risk for seizures following administration of a psychedelic.[23] Results from clinical studies are seldom binary, and the subtleties of which symptoms improve and what safety issues emerge in each specific patient population will be needed to determine any standard of care. One safety issue for most hallucinogenic psychoplastogens is the potential for cardiovascular issues associated with 5-HT2B receptor agonism.[24] Infrequent administration of classic psychedelics may mitigate these issues, but the safe dosing interval for these compounds remains to be firmly established. Many nonhallucinogenic psychoplastogens have been engineered to lack 5-HT2B receptor agonism, providing an additional layer of safety extending beyond central nervous system effects.

Yaden, Earp, and Griffiths argue that patient autonomy is important,[25] and we agree. However, they imply that given the choice between a hallucinogenic and a nonhallucinogenic psychoplastogen, most individuals would choose to undergo psychedelic-assisted psychotherapy because these experiences are often reported as being among the most meaningful experiences of people's lives.[26,27,28,29] However, many of the participants in these studies were "interested in developing their spiritual lives" and were attracted to a study about the effects of a "psychoactive substance used sacramentally." Thus, these participants may have been seeking meaning in their lives or were primed for a transcendental experience, and thus, might not be representative of the general population. Many patients may not want to take a hallucinogen under any circumstance. A recent study suggests that 20% of the population would refuse psychedelic-assisted psychotherapy even if it was recommended by a physician.[30] Furthermore, psychedelic experiences may produce long-lasting effects on a person's personality and worldview,[31,32,33] which could be an unattractive prospect to some patients. Although we do think that hallucinogenic psychoplastogens should be available to patients if proven safe and effective, we do not believe physicians have a "duty to promote" psychedelic use to patients who have strong personal, moral, ethical, or religious objections to the use of hallucinogenic drugs.

Besides an obligation to ensure that the treatments we provide are safe, the concept of positive morality instructs us to develop treatments that "do good." Yaden, Earp, and Griffiths argue that in addition to relieving disease symptoms, hallucinogenic psychoplastogens provide the added benefit of bringing meaning to a patient's life, and thus, might be preferable treatment options from the perspective of positive morality.[34] However, does this argument hold if such a putative benefit is not equitable and

only available to a select few? In addition to a large number of patients who will likely be prohibited from receiving hallucinogenic psychoplastogens due to various medical exclusion criteria, an even larger number of patients could be prevented from taking advantage of hallucinogenic psychoplastogens due to their costs.[35] In order to maximize safety, these medicines must be administered in the clinic under the supervision of one or more healthcare professionals, which drastically increases costs and reduces scalability. Given these economic considerations and the fact that nearly one in five people will suffer from a neuropsychiatric disease at some point in their lifetime,[36] it is unlikely that traditional insurance will reimburse for hallucinogenic medicines used as first-line treatments. Moreover, many patients will not be able to afford taking time off work to travel to clinics appropriately staffed for administering psychedelic-assisted psychotherapy. In fact, an equity gap has already started to emerge following the approval of the hallucinogenic psychoplastogen ketamine for depression.[37] Wealthy individuals have greater access to ketamine treatment because they can afford to pay for the medicine out of pocket and take time off of work to receive in-clinic treatment.

We believe that we have an ethical obligation to ensure that patients in need of psychoplastogenic medicines have access to them. Medicine should alleviate the suffering of all, not simply those who can afford to pay for treatments out of pocket. When we consider the scope of our current mental health crisis, it becomes evident that we need effective, affordable, and scalable treatment options. From that perspective, nonhallucinogenic psychoplastogens have the potential to democratize access to this new class of powerful medicines.

Yaden, Earp, and Griffiths appear to be concerned that if hallucinogenic psychoplastogens do not become the standard of care, they will be "withheld" from patients.[38] We do not share this concern and believe that hallucinogenic psychoplastogens will be appropriately inserted into a treatment hierarchy as more clinical data are gathered. We suspect that more scalable treatment options, such as nonhallucinogenic psychoplastogens, will be among the first medicines received by patients. Unlike traditional antidepressants, nonhallucinogenic psychoplastogens exhibit rapid onset in preclinical models, and thus, it is likely that their effectiveness in patients will be determined quickly. Moreover, if psychotherapy paired with a psychoplastogenic medicine demonstrates substantially greater efficacy than administration of a psychoplastogen alone, a nonhallucinogenic variant capable of being administered in the home would increase patient access by opening doors to telehealth options for pharmacologically enhanced psychotherapy. If patients' symptoms persist, hallucinogenic psychoplastogens will likely still be an option to them.

Yaden, Earp, and Griffiths argue that administration of psychedelics can endow patients with additional meaning in their lives.[39] However, 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. Thus, this argument appears to be outside the scope of medicine and is perhaps more relevant to a discussion about whether all individuals should be allowed to use psychedelics for personal growth and betterment.

At the present time, the true risk/benefit ratios of hallucinogenic and nonhallucinogenic psychoplastogens are not known for various patient populations. Thus, it is too early to declare a standard of care. Any standard of care will be determined empirically by a complex, multivariable equation involving efficacy, safety, and cost-effectiveness. Moreover, the standard of care will evolve as new, real-world clinical data emerge. Indeed, the Research Domain Criteria (RDoC) initiative[40] may result in a separate nosology with yet different standards of care. Thus, declaring one standard of care for multiple patient populations *a priori* is premature. Hopefully, as patient responses are categorized, biomarkers will be discovered to help guide more personalized treatment options. As is typical, the standard of care could involve combinations of treatments, potentially including the measured use of both hallucinogenic and nonhallucinogenic psychoplastogens in the same patient.

We have an ethical obligation to ensure that no viable treatment options are withheld from patients and that medicine is distributed equitably. Our goal should be to mitigate risks while maximizing benefit to patients and society. Thus, we expect that first-line treatments will exhibit a high level of efficacy, present low levels of risk, and be cost-effective as well as accessible. If those medicines prove ineffective, patients should have access to less scalable, higher-risk options. Given the magnitude of our current worldwide mental health crisis, we should not discount any viable

treatment option. We believe that both hallucinogenic and nonhallucinogenic psychoplastogens have important roles to play in alleviating human suffering, but without extensive real-world clinical data in multiple patient populations, it is premature to determine where exactly they will fit in the treatment hierarchy.

Conflict of Interest. K.R. is an employee and serves as the Chief Scientific Officer of Delix Therapeutics, Inc. D.E.O. is a cofounder of Delix Therapeutics, Inc. and serves as the Chief Innovation Officer and Head of the Scientific Advisory Board.

Notes

1. Dos Santos RG, Hallak JEC. Therapeutic use of serotoninergic hallucinogens: A review of the evidence and of the biological and psychological mechanisms. *Neuroscience & Biobehavioral Reviews* 2020;**108**:423–34.
2. Barrett FS, Doss MK, Sepeda ND, Pekear JJ, Griffiths RR. Emotions and brain function are altered up to one month after a single high dose of psilocybin. *Science Report* 2020;**10**:2214.
3. Ly C, Greb AC, Cameron LP, Wong JM, Barragan EV, Wilson PC, *et al.* Psychedelics promote structural and functional neural plasticity. *Cell Reports* 2018;**23**:3170–82.
4. Shao LX, Liao C, Gregg I, Davoudian PA, Savalia NK, Delagarza K, *et al.* Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron* 2021;**109**:2535–44.e4.
5. Yaden DB, Griffiths RR. The subjective effects of psychedelics are necessary for their enduring therapeutic effects. *ACS Pharmacology & Translational Science* 2020;**4**:568–72.
6. Olson DE. The subjective effects of psychedelics may not be necessary for their enduring therapeutic effects. *ACS Pharmacology & Translational Science* 2020;**4**:563–7.
7. Dunlap LE, Azinfar A, Ly C, Cameron LP, Viswanathan J, Tombari RJ, *et al.* Identification of psychoplastogenic N,N-dimethylaminoisotryptamine (isoDMT) analogues through structure–activity relationship studies. *Journal of Medicinal Chemistry* 2020;**63**:1142–55.
8. Cameron LP, Tombari RJ, Lu J, Pell AJ, Hurley ZQ, Ehinger Y, *et al.* A non-hallucinogenic psychedelic analogue with therapeutic potential. *Nature* 2021;**589**:474–9.
9. Dong C, Ly C, Dunlap LE, Vargas MV, Sun J, Hwang I-W, *et al.* Psychedelic-inspired drug discovery using an engineered biosensor. *Cell* 2021;**10**:2779–92.e18.
10. Cao D, Yu J, Wang H, Luo Z, Liu X, He L, *et al.* Structure-based discovery of nonhallucinogenic psychedelic analogs. *Science* 2022;**375**:403–11.
11. Yaden DB, Earp BD, Griffiths RR. Ethical issues regarding non-subjective psychedelics as standard of care. *Cambridge Quarterly of Healthcare Ethics* 2022;**31**(4):464–71.
12. Olson DE. Psychoplastogens: A promising class of plasticity-promoting neurotherapeutics. *Journal of Experimental Neuroscience* 2018;**12**:1–4.
13. Nierenberg AA, Keefe BR, Leslie VC, Alpert JE, Pava JA, Worthington JJ, *et al.* Residual symptoms in depressed patients who respond acutely to fluoxetine. *Journal of Clinical Psychiatry* 1999;**60**(4):221–5.
14. See note 11, Yaden et al. 2022.
15. See note 11, Yaden et al. 2022.
16. Carbonaro TM, Bradstreet MP, Barrett FS, MacLean KA, Jesse R, Johnson MW, *et al.* Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *Journal of Psychopharmacology* 2016;**30**(12):1268–78.
17. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, *et al.* Trial of psilocybin versus escitalopram for depression. *New England Journal of Medicine* 2021;**384**:1402–11.
18. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, *et al.* Effects of psilocybin-assisted therapy on major depressive disorder: A randomized clinical trial. *JAMA Psychiatry* 2021;**78**:481–9.
19. Nishimura A, Aritomi Y, Sasai K, Kitagawa T, Mahableshwarkar AR. Randomized, double-blind, placebo-controlled 8-week trial of the efficacy, safety, and tolerability of 5, 10, and 20 mg/day vortioxetine in adults with major depressive disorder. *Psychiatry and Clinical Neurosciences* 2018;**72**:64–72.
20. Jain R, Mahableshwarkar AR, Jacobsen PL, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *International Journal of Neuropsychopharmacology* 2013;**16**:313–21.

21. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology* 2006;**187**(3):268–83.
22. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. *Psychopharmacology* 2011;**218**(4):649–65.
23. Nayak SM, Gukasyan N, Barrett FS, Erowid E, Erowid F, Griffiths RR. Classic psychedelic coadministration with lithium, but not lamotrigine, is associated with seizures: An analysis of online psychedelic experience reports. *Pharmacopsychiatry* 2021;**54**(5):240–5.
24. Elangbam CS, Job LE, Zadrozny LM, Barton JC, Yoon LW, Gates LD, *et al.* 5-hydroxytryptamine (5HT)-induced valvulopathy: Compositional valvular alterations are associated with 5HT2B receptor and 5HT transporter transcript changes in Sprague–Dawley rats. *Experimental and Toxicologic Pathology* 2008;**60**(4–5):253–62.
25. See note 11, Yaden et al. 2022.
26. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, *et al.* Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology* 2016;**30**(12):1181–97.
27. Griffiths RR, Johnson MW, Richards WA, Richards BD, Jesse R, MacLean KA, *et al.* Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. *Journal of Psychopharmacology* 2018;**32**(1):49–69.
28. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. *Psychopharmacology* 2011;**218**(4):649–65.
29. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology* 2006;**187**(3):268–83.
30. Corrigan K, Haran M, McCandliss C, McManus R, Cleary S, Trant R, *et al.* Psychedelic perceptions: Mental health service user attitudes to psilocybin therapy. *Irish Journal of Medical Science* 2021; **xx**:1–13. doi:10.1007/s11845-021-02668-2.
31. Nour MM, Evans L, Carhart-Harris RL. Psychedelics, personality and political perspectives. *Journal of Psychoactive Drugs* 2017;**49**(3):182–91.
32. Bouso JC, Dos Santos RG, Alcázar-Córcoles MÁ, Hallak JE. Serotonergic psychedelics and personality: A systematic review of contemporary research. *Neuroscience & Biobehavioral Reviews* 2018;**87**:118–32.
33. Forstmann M, Sagioglou C. Lifetime experience with (Classic) psychedelics predicts pro-environmental behavior through an increase in nature relatedness. *Journal of Psychopharmacology* 2017;**31**:975–88.
34. See note 11, Yaden et al. 2022.
35. Vargas MV, Meyer R, Avanes AA, Rus M, Olson DE. Psychedelics and other psychoplastogens for treating mental illness. *Frontiers in Psychiatry* 2021;**12**:727117. doi:10.3389/fpsyt.2021.727117.
36. Available at https://www.nimh.nih.gov/health/statistics/mental-illness (last accessed 28 Feb 2022).
37. See note 35, Vargas et al. 2021, at 12.
38. See note 11, Yaden et al. 2022.
39. See note 11, Yaden et al. 2022.
40. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine* 2013;**11**:126.

Cite this article: Rasmussen K and Olson D. E (2022). Psychedelics as Standard of Care? Many Questions Remain. *Cambridge Quarterly of Healthcare Ethics* 31: 477–481, doi:10.1017/S096318012200010X