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Comment and Response: (Lugo-Radillo & Cortez-Lopez, 2020) Long-Term Amelioration of OCD Symptoms in a Patient with Chronic Consumption of Psilocybin-Containing Mushrooms

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Authors

Fitzpatrick, Ciarán Martin
Anderson, Brian T
Agin-Liebes, Gabrielle
et al.

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Comment and Response: (Lugo-Radillo & Cortez-Lopez, 2020) Long-term Amelioration of OCD Symptoms in a Patient with Chronic Consumption of Psilocybin-containing Mushrooms.

Authors:

Ciarán Martin Fitzpatrick

Brian T. Anderson

Gabrielle Agin-Liebes

Joseph Guydish

Editor's Note:

The Journal of Psychoactive Drugs published a case study reporting reduction of obsessive-compulsive disorder (OCD) symptoms after consumption of psilocybin-containing mushrooms (Lugo-Radillo & Cortes-Lopez, 2021). We subsequently received a letter suggesting that psychedelic research has progressed beyond case studies, and recommending that journals focus on publication of clinical trials rather than case reports. I found the both the letter and the reviewer comments thoughtful and informative concerning current issues in psychedelic research, and invited all authors to publish their comments in this section.

Joseph Guydish, PhD
Editor, Journal of Psychoactive Drugs

Letter to the Editor: Prioritize Well-Controlled Randomized Trials in Psychedelic Medicine

I read with interest the case report entitled “Long-term Amelioration of OCD Symptoms in a Patient with Chronic Consumption of Psilocybin containing Mushrooms”, published in *Journal of Psychoactive Drugs* (Lugo-Radillo & Cortes-Lopez, 2021). While the topic is relevant and provides insights, this study underscores the need for well-controlled clinical trials when evaluating the potential therapeutic efficacy of psychedelics such as psilocybin and lysergic acid diethylamide (LSD).

Psychedelic medicine is undergoing a renaissance, after many decades of limited research as a consequence of political forces. Despite being generally considered physically safe and non-addictive, these psychoactive substances significantly alter cognitive, mood, and perceptual processes (Nichols, 2016). In this past decade, emerging clinical research has revealed positive effects of psychedelic-assisted psychotherapy on anxiety, addictive and depressive symptoms. Most noteworthy, London’s Centre for Psychedelic Research demonstrated anti-depressant effects of psilocybin equal to escitalopram in phase 2, double-blind, randomized controlled trial. Positive treatment outcomes favoured psilocybin involving these patients with major depressive disorder (Carhart-Harris et al., 2021).

What the psychedelic community needs are well-designed clinical trials, not more case reports. James Allen Wilcox reported in this journal’s 2014 issue that psilocybin relieved core symptoms of OCD in one patient, but there was a future “need for further, legitimate research into the value of psilocybin in the treatment of anxiety disorders” (Wilcox, 2014). That time for legitimate research is now, as jurisdictions loosen laws and there are 176 “recruiting and not yet recruiting studies” registered on ClinicalTrials.gov (2021). This plethora of ongoing psychedelic-based interventions is in stark contrast to other previously published cases (Leonard & Rapoport, 1987; Moreno & Delgado, 1997; Wilcox,

2014), when funding and ethical approvals were hard to come by for researchers.

The medical community does not need more cases reporting preventative or therapeutic interventions in small sample sizes, e.g. *n=1,* as these require stronger evidence. Lugo-Radillo & Cortes-Lopez detailed a patient “who reported a significant decrease in his OCD symptoms after the consumption of psilocybin-containing mushrooms” (2021). This positive case may act as a guide for vulnerable patients wishing to re-create this outcome, and the variant and source of mushrooms are even identified here. The inclusion of such information may exert more harm than good, as the field awaits news of trustworthy and possible guideline-changing clinical trial data.

Psilocybin has been once safely used in patients with OCD in a clinically controlled environment (Moreno, Wiegand, Taitano, & Delgado, 2006), but nothing can be inferred to non-clinically controlled environments. Meanwhile, it is widely known psychedelics induce hallucinations, which can result in prolonged adverse reactions including Hallucinogen Persisting Perception Disorder (Breakey, Goodell, Lorenz, & McHugh, 1974; Fink, Simeon, Haque, & Itil, 1966; Halpern, Lerner, & Passie, 2018; Litjens, Brunt, Alderliefste, & Westerink, 2014; Vardy & Kay, 1983).

This author expects the main criticisms of this Letter to be: i) there are already case reports published on using psychedelics to treat psychiatric illnesses; and ii) there should be freedom of speech to let the public decide their best course of action. The psychedelic research community should shun anecdotal case reports and instead, embrace the opportunity to plan and execute randomized controlled trials investigating psychedelic therapies.

As clinical scientists, we owe our communities thorough study designs, rigorous analyses, and transparent dissemination of promising breakthroughs,

limitations and null hypotheses. In this past, it was not possible to carry out clinical trials testing psychedelics, and anecdotal evidence was ultimately published in respected, peer-reviewed journals. Our field should seek to transition in this new era of evidence-based medicine that we have earned to benefit society - patients deserve that care and protection.

Ciarán Martin Fitzpatrick
BMC Series, 4 Crinan Street, London, N1 9XW, United Kingdom.
Email: Ciaran.fitzpatrick16@gmail.com; Tw: @CiarnMartinFit1; ORCID: 0000-0002-9996-4541

Reviewer 1 Comments: In defense of case reports in psychedelic medicine

This Letter to the Editor sheds light on the important role that randomized controlled trials (RCTs) have to play in the developing field of psychedelic medicines. In response to the case report by Lugo-Radillo and Cortes-Lopez (2021) in the journal, the author correctly encourages members of the psychedelic biomedical research community to prioritize RCTs as a rigorous means of testing the efficacy of psychedelics, like psilocybin, for the treatment of medical conditions. Ultimately, this is a call for evidence-based medicine in regards to psychedelic therapies.

All of these points are laudable, but I'm afraid the particular arguments of the letter do not accomplish its aims.

For any clinical research data to be 'legitimate', they must be reported transparently and appropriately. For example, the Phase 2 trial of psilocybin vs escitalopram cited by the author is not correctly represented in this Letter. This trial failed to demonstrate efficacy of psilocybin over escitalopram with its primary clinical outcome, and while the secondary outcomes tended to favor psilocybin, per the trial’s own published report, “the confidence intervals for the between-group differences were not adjusted for multiple comparisons, and no

conclusions can be drawn from these data” (Carhart-Harris et al., 2021). Also, given’s the trial’s design and a negative primary outcome, the data should not be used to claim equivalence of effect either (Gewandter et al., 2017). Sober interpretation of data is as important for RCTs as it is for case reports.

While it is certainly true that RCTs provide a stronger form of evidence than case reports, it is not clear that, as the author claims, "the medical community does not need more cases reporting preventative or therapeutic interventions.” The report of Lugo-Radillo and Cortez-Lopez contributes something rather significant for the field -- the patient-reported outcomes of 6-months of self-medication with psilocybin-containing mushrooms every 2 weeks. No modern trial of psilocybin therapy to date has come close to administering psilocybin up to 12 times to a participant over 6 months, and such a trial would likely be very expensive and unlikely to be conducted anytime soon. Why should we not share such observational data (even with its many limitations) as a means of raising novel clinical questions and generating hypotheses that may someday be addressed by more rigorous methods?

It is true that publishing the species, genus and dose of a natural product could lead vulnerable patients to attempt to self-medicate, and that this could have negative outcomes (Giancola, Korson, Caplan, & McKnight, 2021). However, publishing the dose and administration route of synthetic prescription drugs may also lead individuals to self-medicate and harm themselves. We see this, sadly, all the time with non-prescription opioid use, but we do not suggest that investigators cease publishing the dose of fentanyl they used in their clinical reports. Moreover, this idea seems to overlook the potential benefits of learning from detailed case reports such as Lugo-Radillo and Cortes-Lopez's manuscript when RCT data are not available. Clinical providers in places like Oregon, where psilocybin therapy will soon be legal by state law, will need all the data they can

access to make informed treatment decisions with their patients in the absence of evidence-based guidelines.

Finally, the claim that research funding and ethical approvals are now easier to come by is not consistently true outside of Europe, the USA, and some other high-income countries. In recent years, Mexican colleagues of mine have continued to have difficulty obtaining regulatory approvals and funding for conducting clinical research with psychedelics. Lugo-Radillo & Cortes-Lopez should be thanked for contributing their case report to the scientific literature on psilocybin; and more rigorous, observational data from Oaxaca, the 'birthplace' of psilocybin science should be encouraged. Suggesting that the psychedelic biomedical research community should "shun anecdotal case reports" overlooks a gross inequity in access to academic resources that could limit the inclusion of more diverse perspectives in psychedelic science, and especially from areas of the world that have long-standing traditions of use of psychedelic natural products, and wherefrom biomedical investigators likely have much to learn.

Brian T. Anderson, MD, MSc
Department of Psychiatry and Behavioral Sciences
University of California San Francisco
brian.anderson@ucsf.edu

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Reviewer 2 Comments: A case for integrating nomothetic and idiographic methodologies in psychedelic research

This is an interesting and thought-provoking letter to the editor. I appreciate Fitzpatrick’s concerns about the need for rigorous scientific practice and accurate representation of the risks and harms associated with psilocybin use in the scientific literature. However, Fitzpatrick’s letter overemphasizes these

relative risks and underemphasizes the valuable clinical data offered in the Lugo-Radillo and Cortes-Lopez case report.

The psychedelic research community certainly carries an ethical responsibility to pursue balanced research that assess both the benefits and harms associated with psychedelics use. However, Fitzpatrick neglects to cite any of the authoritative papers in the literature that report on safety guidelines and that warn against use in uncontrolled non-medical settings e.g., (Johnson, Richards, & Griffiths, 2008). He also fails to accurately represent the risks for Hallucinogen Persisting Perception Disorder (HPPD) and other potential psychiatric harms (e.g., prolonged psychosis or injuries). While the rates are non-trivial, epidemiological data indicate that rates of adverse effects are very low relative to the adverse effects of other psychoactive drugs. In population-data research, lifetime psychedelic use has not been associated with any significant psychiatric symptom indicators, and studies have associated psychedelic use with significantly reduced odds of mental health problems (Carhart-Harris & Nutt, 2010; Johansen & Krebs, 2015; Nutt, King, & Phillips, 2010). Nevertheless, clinicians and researchers should provide patients adequate psychoeducation about these risks. Indeed, Lugo-Radillo and Cortes-Lopez explained in their report that they “warned [their patient] about the potential danger of taking” psilocybin in this unsupervised context.

Lugo-Radillo and Cortes-Lopez developed a thoughtful case report that offers clinically meaningful and prospective longitudinal data deserving of publication. While randomized controlled trials (RCTs) represent the current gold-standard study design for the determination of the efficacy and safety of clinical interventions, case reports serve an important complementary role and have been invaluable in the progress of medical science. Obsessive Compulsive Disorder (OCD) is a particularly debilitating and intractable psychiatric condition

for which there is a strong need for innovative treatments. Despite the growing medical promise of psychedelics, clinical trials are time-consuming (up to several years), and require a massive number of resources, which greatly limits the rate at which clinical information becomes available to the medical and scientific community. Many of the clinical observations described in Lugo-Radillo and Cortes-Lopez's report would have been uncaptured in modern RCTs as they are conducted under highly controlled and idealized conditions that reduce their generalizability to complex 'real-world' scenarios. For example, the patient reportedly consumed psilocybin concurrently with prescribed psychotropic medication over the course of several months, which would have been a primary exclusion in any RCT. Furthermore, in pharmacotherapy research, nomothetic, group-level paradigms have been traditionally prioritized, which can undermine the understanding of key individual factors and variations. The data generated from case reports can support NIH precision medicine initiatives (Insel, 2014) that call for more nuanced and individualized treatment protocols to complement population-focused treatment models. Lastly, Fitzpatrick points out that additional RCTs in this area are needed but does not mention that there are three ongoing RCTs examining the effects of psilocybin in OCD populations (NCT03300947, NCT03356483, NCT04882839). Hopefully, the scientific medical community will embrace an integration of these research methods to support the development of best evidence-based practices to address the devastating impact of OCD and worsening global mental health crisis.

Gabrielle Agin-Liebes, PhD
Department of Psychiatry and Behavioral Sciences
University of California San Francisco
Gabrielle.agin-liebes@ucsf.edu

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