Mush room for improving therapeutic approaches in psychiatry

Graaf, P.H. van der

Mush Room for Improving Therapeutic Approaches in Psychiatry

Piet H. van der Graaf[1,2,*]

In the televised fictional drama "Nine Perfect Strangers," based on a novel with the same name,[1] nine people gather for a retreat in a wellness resort which promises to heal and transform them. The guests discover that as part of the program the charismatic owner of "Tranquillum" has been feeding them smoothies spiked with psilocybin-containing mush room extract without their knowledge. After the initial obvious outrage over the absence of informed consent, the guests are then left with the question whether to continue with this unconventional therapeutic approach, which at least for some of them seemed to have had beneficial effects. Or had it? Although single-blinded at the start, this fictional experiment of course suffered from so many shortcomings that it was impossible to tell. This is perhaps somewhat reflective of the limitations of many actual psilocybin trials in the real world (133 were listed in ClinicalTrials.gov at the time of writing this Editorial[2]): small *n* numbers, absence of placebo and/or comparator, short duration, and lack of objective end points to name a few. Recently, however, a year after the release of the series, results were reported of the most extensive phase II clinical trial investigating psilocybin in treatment-resistant major depressive disorder.[3] The results (which can be summarized as "both intriguing and sobering"[4]) were widely reported in the media along the lines of "magic mush room for depression" and triggered the start of a phase III study,[2,5] which should provide the most conclusive results about psilocybin's potential therapeutic benefit to date.

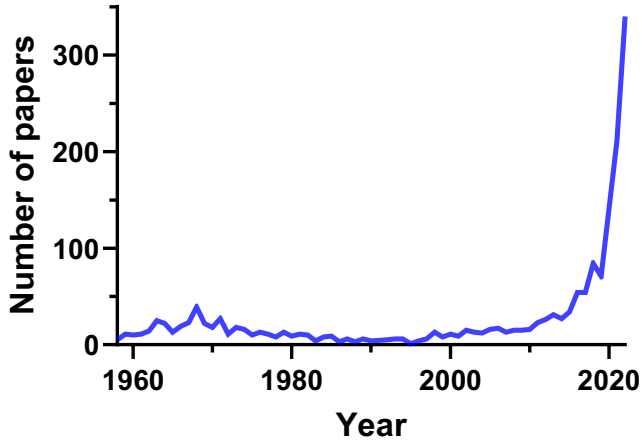

Figure 1 Number of publications referring to psilocybin per year as identified by PubMed.[7]

[1]Certara, Canterbury, UK; [2]University of Leiden, Leiden, The Netherlands. *Correspondence: Piet H. van der Graaf (piet@certara.com)

Received January 30, 2023; accepted January 30, 2023. doi:10.1002/cpt.2859

Figure 2 *Clinical Pharmacology & Therapeutics* April 2023 cover image: Mush room for improving therapeutic approaches in psychiatry.

The clinical pharmacology of psilocybin was already reviewed in this journal six decades ago ago,[6] but interest from the scientific and clinical community seems to have gathered serious momentum only in the last 5 years (**Figure 1**). This has occurred alongside a broader resurgence of research into therapeutic applications of psychedelic agents.[8,9] As in every other area of drug development, the involvement of clinical pharmacology will be a key determinant of success and *Clinical Pharmacology & Therapeutics* (*CPT*) expects to see an increase in submissions and publications in this area. Recent examples are the reports on pharmacokinetics–pharmacodynamics (PKPD) of lysergic acid diethylamide (LSD) microdosing[10] and PKPD interactions between psilocybin and escitalopram.[11] In this issue of *CPT* (**Figure 2**), the same group from the University of Basel now describes the PKPD of psilocybin in healthy volunteers and the impact of covariates, specifically body weight.[12] Such studies are essential to support the optimal design of further clinical studies of psilocybin and other therapeutic psychedelics. They illustrate the critical role of clinical pharmacology as an enabler to convert medical hypotheses into safe and effective therapeutics to improve patients' lives.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST
The author declared no competing interests for this work.

1. Moriarty, L. Nine Perfect Strangers (Flatiron Books, New York, NY, 2018).
2. ClinicalTrials.gov. Search results for psilocybin <https://clinicaltrials.gov/ct2/

results?cond=&term=psilocybin&cntry=&state=&city=&dist=>. Accessed January 30, 2023.
3. Goodwin, G.M. *et al*. Single-dose psilocybin for a treatment-resistant episode of major depression. *N. Engl. J. Med.* **387**, 1637–1648 (2022).
4. Madras, B.K. Psilocybin in treatment-resistant depression. *N. Engl. J. Med.* **387**, 1708–1709 (2022).
5. King's College London. Largest trial to date shows that psilocybin reduces depression symptoms <https://www.kcl.ac.uk/news/largest-trial-to-date-shows-that-psilocybin-reduces-depression-symptoms> (2022). Accessed January 12, 2023.
6. Jacobsen, E. The clinical pharmacology of the hallucinogens. *Clin. Pharmacol. Ther.* **4**, 480–503 (1963).
7. National Library of Medicine. Search results for psilocybin <https://pubmed.ncbi.nlm.nih.gov/?term=psilocybin&sort=pubdate>. Accessed January 30, 2023.
8. Ko, K., Kopra, E.I., Cleare, A.J. & Rucker, J.J. Psychedelic therapy for depressive symptoms: a systematic review and meta-analysis. *J. Affect. Disord.* **322**, 194–204 (2023).
9. Marwaha, S., Palmer, E., Suppes, T., Cons, E., Young, A.H. & Upthegrove, R. Novel and emerging treatments for major depression. *Lancet* **401**, 141–153 (2022).
10. Holze, F. *et al*. Pharmacokinetics and pharmacodynamics of lysergic acid diethylamide microdoses in healthy participants. *Clin. Pharmacol. Ther.* **109**, 658–666 (2021).
11. Becker, A.M. *et al*. Acute effects of psilocybin after escitalopram or placebo pretreatment in a randomized, double-blind, placebo-controlled, crossover study in healthy subjects. *Clin. Pharmacol. Ther.* **111**, 886–895 (2022).
12. Holze, F., Becker, A.M., Kolaczynska, K.E., Duthaler, U. & Liechti, M.E. Pharmacokinetics and pharmacodynamics of oral psilocybin administration in healthy participants. *Clin. Pharmacol. Ther.* **113**, 822–831 (2023).