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## Pharmacological and Nonpharmacological Components of Psychedelic Treatments: The Whole is Not the Sum of the Parts

To the Editor: The commentary by Goodwin and colleagues (1) concludes that "the effects observed thus far in the best controlled studies of psychedelic treatment must be attributed to the drug itself and not to psychotherapy." However, none of the trials cited in the commentary elucidates the specific contribution of the psychotherapy or the medication because, within each of these studies, all participants received the same regimen of nonpharmacologic treatment (here labeled NPT to avoid argument about what constitutes "psychotherapy"). For the same reason, we cannot draw any conclusion about the effect of the medication itself, independent of the NPT. To isolate these effects, it is necessary to manipulate both the NPT and the medication conditions, e.g. (in the simplest case), by using a two-by-two factorial trial design. Then we can estimate the contribution of the drug, the NPT, and the drug-by-NPT interaction to the results of the trial.

The authors also maintain that including psychotherapy in studies of psychedelics, beyond what is necessary to ensure "psychological and physical safety," will complicate drug approval. But regulatory bodies such as the FDA understand that safety and efficacy can depend on the therapeutic context. For example, pivotal trials of extended-release naltrexone for both alcohol use disorder and opioid use disorder included 12 sessions of manualized individual disorder-specific therapy (2, 3). As a result, the label for extended-release naltrexone states that it "should be part of a comprehensive management program that includes psychosocial support." (4) The label does not prescribe the type or the amount of NPT.

As noted in the commentary and elsewhere, there are several scientific challenges and clinical risks of particular concern with psychedelic treatments, though not unique to them. These issues heighten the importance of attending to the role of NPT in psychedelic treatment. While there is little evidence to support the use of one "brand" of NPT over another in any of the indications currently being studied, the relative safety of psychedelics in studies to date has been demonstrated only in the context of robustly implemented NPT.

In clinical practice, effectiveness depends on the overall effect of the combined treatment, which is the sum of the drug effect, the NPT effect, and the interaction between the two. Even if the drug and the NPT by themselves are useless but the combination is highly effective, we could have an important new treatment. The possibility of such interactions is as much an opportunity as a challenge.

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**Michael P. Bogenschutz, M.D.**

*Department of Psychiatry, NYU Grossman School of Medicine, New York.*

*Send correspondence to Dr. Bogenschutz (michael.bogenschutz@nyulangone.org).*

*Dr. Bogenschutz reports research support from B.More, Inc., Dr. Bronner's Family Foundation, the Fournier Family Foundation, the Heffter Research Institute, Bill Linton, Mind Medicine, Inc., the Multidisciplinary Association for Psychedelic Studies (MAPS) PBC, the Riverstyx Foundation, Tilray Canada, and the Turnbull Family Foundation. He has consulted for the Heffter Research Institute, and currently serves on the advisory boards of Ajna Labs LLC, Bright Minds Biosciences, Inc., and Journey Colab.*

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## Is Poorly Assisted Psilocybin Treatment an Increasing Risk?

To the Editor: In the July 2023 commentary, "Must Psilocybin Always 'Assist Psychotherapy'?" (1) Goodwin et al. raised interesting questions about paradigms for the therapeutic use of psychedelics. These substances are already applied in diverse ways, from community and relational Indigenous practices (2) to uses deemed "recreational" but which also include self-treatment (3, 4). Thus, while psychedelics indeed need not always "assist psychotherapy," interactive elements with the substance's effects have been deemed essential for safety and efficacy across a variety of existing paradigms.

However, the assertions that the intervention used in the phase 2 trial referred to by the authors (5) are "simply ensuring, as is intended, psychological and physical safety" and that it "is applied in a stereotyped way, whatever the drug dose," as distinct from psychedelic-assisted (psycho) therapy (PAT), where "complex interaction with a therapist during

the active drug experience clearly complicates interpretation," merit further scrutiny. The minimum necessary procedures to prevent harms should be distinguished from PAT. Conversely, there are striking similarities in the guiding principles of the therapist training for this trial (6) with those of PAT models. While not all of these studies have released a manual, some, such as MAPS and Yale, have (7, 8). To the best of our knowledge, the manual for the COMPASS phase 2 trial has not been made publicly available, thereby limiting detailed comparisons. Compounding these issues are potential biases and conflicts of interest involved in developing a proprietary synthetic formulation of psilocybin, which not only raises ethical concerns regarding Indigenous rights (9), but could potentially influence efforts to more easily bring a drug to market by downplaying the role of therapy. Critically, we submit that this role includes optimizing both safety as well as efficacy in relational processes which cannot be treated independently of the drug effect itself (10).

The occurrences of suicidal ideation and related behaviors in the largest clinical trial with a psychedelic to date (5) suggests that careful consideration of the PAT concept may result in safer approaches. It seems reasonable to speculate that higher rates of serious adverse events in the 25 and 10 mg psilocybin groups might have been mitigated with greater emphasis on relational elements during preparation and integration—rather than simply "psychological support." In addition, cases of boundary violations and abuse (11), correctly highlighted as important issues in PAT (and unfortunately in medicine generally as well [12]), are not, however, justifications for no therapy.

The term "psychedelic-assisted (psycho) therapy" does not intend to "capture the true mechanism of change," but rather to delineate a holistic approach developed over decades, starting with LSD (13). It creates a therapeutic container to prevent unassisted or poorly assisted drug administration. We understand efforts to simplify processes for regulating systems for drug approval and consequent accessibility, but not at the costs of downplaying the complexity of intrapersonal, interpersonal, and contextual processes. Oversimplification is not clarity, and suggesting effectiveness comes only from drug administration may lead to unintended harms.

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**Eduardo Ekman Schenberg, Ph.D.**
**Franklin King IV, M.D.**
**João Eusébio da Fonseca**
**Leor Roseman, Ph.D.**

*Instituto Phaneros, São Paulo, Brazil (Schenberg); Massachusetts General Hospital and Harvard Medical School, Boston (King); Psychotherapist in private practice, Lisbon (Fonseca); Department of Psychology, University of Exeter, Exter, United Kingdom; Centre for Psychedelic Research, Imperial College London, London (Roseman).*

*Send correspondence to Dr. Schenberg (eduardo@institutophaneros.org.br).*


*Dr. Schenberg is Director of Instituto Phaneros, a Brazilian non-profit offering psychedelic-assisted therapy research training and is scientific advisor to investment fund Ocama Partners. Dr. King holds stock in COMPASS and Cybin, has consulted for Cybin in the previous 24 months, and sits on the scientific advisory board of Apex Labs for which he owns stock equity. Mr. Fonseca was one of the lead therapists of the COMPASS trial (COMP 001), done at the Champalimaud Foundation in Portugal between 2020 and 2022. He is a psychotherapist at the Liminal Minds Clinic, providing ketamine-assisted therapy. Dr. Roseman's current research into psychedelic peacebuilding is funded by Christian Angermayer, a significant investor of COMPASS through ATAI Life Sciences.*


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## Psychotherapy in Psychedelic Treatment: Safe, Evidence-Based, and Necessary

To the Editor: We agree with Goodwin et al. (1) that "[it] is important to get this right" when it comes to the role of psychotherapy in psychedelic trials. The precedents set now will have implications for research, regulation, and access to care if these drugs are approved for clinical use. We do not agree, however, with the authors' conclusions about the role of psychotherapy.