Viewpoint

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Studying Harms Is Key to Improving Psychedelic-Assisted Therapy—Participants Call for Changes to Research Landscape

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Although psychedelic drugs generally have good safety profiles, a recent systematic review[1] concluded that adverse events in psychedelic trials are poorly defined, not systematically assessed, and likely underreported. In the past year there have been multiple reports of serious adverse events (SAEs), and long-lasting harms to participants in clinical trials of psychedelic-assisted therapy (PAT) have emerged.[2,3] We draw attention to a unique and overlooked category of risk in PAT stemming from the interactions between therapists and patients receiving high doses of psychedelics. In our view, the understudied therapeutic component of PAT presents the most serious risks. Addressing it requires interdisciplinary approaches by researchers free from conflicts of interests.

Attending to the Therapy in PAT

Psychedelic-assisted therapy combines 2 psychoactive components: drugs and psychotherapy. This innovative combination is theorized to create a synergy that enhances the effects of each component, and it comes with unique challenges and risks. While adverse events are not unique to psychedelic research, it would be unimaginable for clinical trials using a combination of 2 drugs to only examine or regulate one of the 2 components. However, this is the norm in psychedelic research, in which the psychological support is neither systematized nor evaluated as in traditional psychotherapy research. The absence of regulatory infrastructure to adequately monitor both the drug and psychotherapy components creates a situation in

which—if legalized in their current form—unevaluated and potentially harmful practices will be imposed on vulnerable patients seeking PAT.

We outline 2 concerns regarding the psychotherapy component: (1) the lack of empirical evidence for the quality and safety of the psychological support provided during dosing sessions, and (2) the interactions between the drug effects and the psychotherapy.

In the absence of empirically derived and tested psychotherapy practices during dosing sessions, psychedelic therapists follow a set of untested guiding principles based on observations and beliefs from early psychedelic researchers.[4] For example, the use of "nurturing touch" is promoted as a therapeutic tool in PAT. It is a poorly defined term that can include hand-holding or putting a hand on the participant's arm, chest, or back and is intended to provide reassurance, to refocus attention on inner experience, or to satisfy early unmet emotional needs. Researchers have noted that the absence of clear guidelines leaves acceptable forms of touch open to interpretation by therapists and clients, which can lead to boundary violations while clients are in altered states.[5] The use of touch in psychotherapy is controversial and understudied, even without adding psychedelics.

Fundamentally, psychotherapy requires active, ongoing, and dynamic consent. In PAT, patients are under the influence of substances that may enhance suggestibility and impair capacity for consent and withdrawal (which is also restricted by protocol), potentially increasing overcompliance with therapist suggestions. The use of conventional psychotherapy approaches, which require active, ongoing, and dynamic consent, poses unique risks and problems. Even psychotherapy practices with an existing evidence base need to be reevaluated for safety and efficacy in PAT.

SAEs and Harms

In the past year, media stories have identified SAEs and harms—including suicidality, sexual abuse, and psychotic symptoms—in trials sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS) of 3,4-methylenedioxymethamphetamine–assisted therapy for posttraumatic stress disorder.[2,6] The controversy has generated heated arguments that overshadow substantive issues of patient safety. We wish to sidestep questions of blame to highlight how these and other negative participant experiences can help inform future research and therapy protocols. Although psychedelic substances differ in their pharmacological risk-benefit profiles, the risks posed by combining the drugs with untested psychotherapy practices cut across substances.

Suicidality

At least 3 of the 42 participants (7%) from MAPS' first phase 3 trial reported increases in suicidality and suicidal behavior in the 2 months following the primary end point (a 12-month follow-up has yet to be

published).[2,6] A recently published study[3] of psilocybin-assisted therapy for depression similarly found 6.3% and 8% SAEs (suicidal thoughts and behavior; self-injury) in the 25-mg (n=79) and 10-mg (n=75) groups compared with 1.3% in the 1-mg (n=79) control group. These reports—which align with common knowledge about the destabilizing potential of psychedelics—suggest that the posttrial and/or treatment period may be particularly fraught for some, and that current protocols require improvements.

Abuse

Footage released by the media of a phase 2 clinical trial session involving 3,4-methylenedioxymethamphetamine shows therapists pinning down a participant, cuddling and kissing her, and physically overpowering her attempts to resist. Clinical trialists and study sponsors failed in their safety monitoring responsibilities, and the therapists' abuse progressed to sexual exploitation.[2] Although the therapists have been condemned for their actions, these events should be viewed as a catastrophic result of multiple factors currently unaddressed in PAT. These factors include overly flexible therapy protocols, use of unevaluated and controversial practices, increased suggestibility, vulnerability to abuse, and failures in oversight and regulatory mechanisms.

Paradoxical Responses

Three MAPS participants who experienced significant improvements on primary outcome measures also reported decompensation (ie, suicidality, psychotic symptoms) shortly following the trial.[2] This is echoed by recently published testimony from a participant in a psilocybin trial who experienced relief from depression but developed severe anxiety.[7] These paradoxical responses suggest that emerging symptoms may elude short follow-up windows and disorder-specific outcome measures, and that decompensation is occurring even in treatment responders.

Dependency

Participants in MAPS-sponsored clinical trials have reported rapidly developing overdependency on their trial therapists, which they said contributed to subsequent harms.[2] It is imperative that researchers investigate the potential of these treatments to foster dependency. In such cases, extending the treatment period without attending to the risk of dependency may compound harm instead of preventing posttrial decompensation.

A Path Forward for Research

These participant experiences signal to the scientific community that participants are being harmed in psychedelic trials, some of these harms are being missed by existing research protocols, and current reporting pathways and oversight mechanisms are not always functioning as they should. They highlight gaps in

measurements and reporting that point to potential issues in current protocols. The *Lancet Psychiatry* Commission on Psychological Treatments Research in Tomorrow's Science recommends embedding phenomenological explorations of SAEs in trial designs to circumvent detection biases.[8]

Responses to the recent media coverage have generated speculative and polarized debates that distract from sober scientific discussions about potentially preventable harms; concerns have also been raised about financial conflicts of interest[9] and researcher bias.[10] Although we do not question the intentions of individual researchers, this research climate compromises risk assessment and mitigation. To ethically and safely move forward, the field must invite researchers without personal or financial ties to psychedelic medicine to retroactively assess work completed to date, conduct phenomenological research to better understand SAEs and harm, and integrate into research teams that are running clinical trials. Researchers and proponents of PAT must grapple with ethical and methodological issues regarding risk, distress, psychotherapy, informed consent, suggestibility, blinding, and expectancy effects, all of which limit the usefulness of safety and efficacy data.

Conclusions

Research participants who have experienced harm in psychedelic clinical trials, two of whom are authors of this Viewpoint, have a unique epistemic standpoint from which to improve the field. We point to the psychotherapy protocols that accompany psychedelic administration as an understudied and undertheorized source of preventable risk in PAT. If the field fails to attend to this gap, anticipated regulatory approvals will mandate that patients undergo untested and controversial psychotherapy protocols alongside the use of psychedelics. This would expose future patients to unnecessary risk and put clinicians at risk of malpractice if the SAEs reported herein were to occur in their clinical practices. To avert this possibility, researchers must undertake phenomenological research to better understand SAEs, and researchers without personal and financial conflicts of interest must conduct and evaluate research.

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