Must Psilocybin Always "Assist Psychotherapy"?

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Drugs such as psilocybin and many other serotonergic agents can produce a powerful psychedelic experience. It is now commonplace to hear the expression "psychedelic-assisted psychotherapy" or "psychedelic-assisted therapy" when their use in treating mental health conditions is described. Are we clear on what we are trying to describe? Take the definition of psychedelic-assisted therapy offered by a new European organization for psychedelic access and research (1):

> The fundamental therapeutic benefit of PAT [psychedelic-assisted therapy] comes from the combination of psychedelic medicine and therapy. The drug is a catalyst for treatment, not a treatment in itself.… In other words, psychedelics' novel therapeutic value stems from their role as enhancements to a psychotherapeutic process, grounded in a relationship-centered approach, that views mental health through a biopsychosocial lens.

The statement that the drug is a catalyst for treatment, not a treatment in itself, is grounded in an odd dualism. The drug as a medication presumably works on the brain (as a "catalyst"), but there is a separate psychotherapy that it facilitates. That psychotherapy is "relationship centered," which has usually meant nondirective counseling (Table 1). Ironically, there is no evidence that the conditions being targeted by psychedelics (severe depression, posttraumatic stress disorder [PTSD], and substance use disorders) are effectively treated by nondirective counseling. More importantly, the statement fails to recognize that the psychological support provided in recent studies of psilocybin is primarily directed to safety—specifically, the preparation and safeguarding of vulnerable people who are submitting to a potentially disorienting experience. They will also be participating in a clinical trial, which requires informed consent and a measure of equipoise. They do not typically receive evidence-based psychotherapy as it is usually understood. Staff with therapy backgrounds may be an excellent choice of personnel to provide the necessary and essential support, but it is an open question how far their efforts enhance efficacy rather than simply ensuring, as is intended, psychological and physical safety. Such safety creates optimal conditions for patients to be immersed in the psychedelic experience.

It is important to get this right, because regulatory bodies are asked to approve drugs with a defined efficacy and safety, not psychotherapies. Indeed, the drug effect can only be established unambiguously if psychological support is available largely to ensure safety and is applied in a stereotyped way, whatever the drug dose. Any complex interaction with a therapist during the active drug experience clearly complicates interpretation of treatment outcomes; therapist expectations could create conditions ripe for mutual unblinding and the amplification of demand characteristics. Additionally, the harms that can result from the interactions between therapists and patients during a psychedelic experience may not be fully appreciated. Unregulated psychotherapy practice regularly leads to ethical violations (2). The risk that such practice could become the natural partner in "psychedelic-assisted psychotherapy" has been highlighted recently (3). There is therefore nothing to be gained by exaggerating the role of psychotherapy in deriving benefit from the psychedelic experience.

The confusion may lie in large part in the medical history of the drugs that produce psychedelic effects. In the 1950s, virtually all influential psychiatrists in the United States had undergone psychoanalysis and spoke the language of psychodynamic psychotherapy. When Sandoz Laboratories made lysergic acid diethylamide (LSD) available to them, the package insert stated that it was to be "used in analytical psychotherapy to elicit release of repressed material and to provide mental relaxation." The recommended dose was stated to vary greatly from patient to patient, to be built up in small steps (from 25 micrograms) at weekly visits and to anticipate 7–10 such visits in milder cases and 14–15 in more severe cases. What was described as "proper psychiatric supervision" was deemed essential because of the potential for adverse reactions. Thus, the recommendation was explicitly to use relatively low doses of LSD as an aid to psychotherapy, or as a psycholytic, to use the terminology of the time.

However, from early on in the medical use of LSD, there was a competing tradition that used much higher doses and produced states that were intrinsically less amenable to formal interaction with a therapist. The psychiatrist Humphry Osmond, with collaborator Abram Hoffer, had intended to simulate the negative impact of delirium tremens to deter patients' harmful substance use. In fact, the subjective effects were both positive and therapeutic. Osmond coined the term psychedelic (meaning mind manifesting) for the effects

produced by the range of drugs now known to act at the 5-HT_{2A} and other serotonergic receptors (4).

The need for a supportive companion had a different emphasis from the psychotherapeutic interaction implied under the influence of drug in the psycholytic model. In practice, the emphasis came to be placed on preparation, as in development of the right (mind-)set, and an appropriate, safe setting. It is ironic that these innovations are usually attributed to the early influence of Al Hubbard and Timothy Leary. The involvement of these characters, as described in Michael Pollan's influential 2018 book, *How to Change Your Mind: The New Science of Psychedelics* (5), marks the evolution of psychedelic interest away from medicine and into the counterculture of the 1960s. The consequence was a loss of credibility and the withdrawal of interest and funding for clinical research. It eventually led to the banning of the drugs for legal use and the end of quality research on their actual value in psychiatry. It drove underground the use of psychedelic experience as a treatment for mental health conditions. The role of psychological support in these circumstances has been interpreted in very different ways since then, from passive support to potentially exploitative participation in a shared experience (and everything in between). The strict distinction between psycholytic treatment and psychedelic treatment appears largely to have been lost, and the two approaches remain elided as "psychedelic-assisted psychotherapy or therapy" to the present day.

THE RETURN OF THE PSYCHEDELIC MODEL

The reappearance of the psychedelic experience as a mainstream therapeutic asset for patient populations began with an open study of obsessive-compulsive disorder (OCD) using modest doses of psilocybin (6). There followed controlled studies in patients with cancer diagnoses (7–9). Psilocybin at relatively high doses produced typical psychedelic effects, including increased connectedness, visual restructuration, and emotional reexperiencing of past events (10). The focus on cancer patients meant that there were particular claims for effects on the demoralization wrought by imminent death. However, the effects on mood and anxiety were also striking for their rapid onset and large size on standard scales.

While the choice of cancer patients made generalization difficult (11), a pilot study in treatment-resistant depression by the Imperial College London group (12) brought a more conventional focus to the application of psychedelic doses of psilocybin. It demonstrated that the administration of psilocybin (at 10 mg and 25 mg) to patients with moderate or severe depression appeared to be safe and well tolerated. Building on this experience, the COMPASS Pathfinder–sponsored phase 2 study (COMP 001) with investigational drug COMP360 (a proprietary synthetic psilocybin formulation) recruited 233 patients with treatment-resistant depression at 22 sites in 10 countries (13). Patients and sites were largely naive to psychedelics. Effects on mood were immediate and showed a dose-response relationship, with clear separation of the highest dose (25 mg) from the lowest (1 mg), with 10 mg being intermediate. Since expectation and psychological support were equal across doses, psilocybin behaved as an active drug would be expected to behave.

PSYCHOLOGICAL SUPPORT

Preparation is the key function of the sessions leading to drug administration. Why would you not prepare a naive patient for exposure to a drug that can produce an extreme emotional experience, both positive and negative? Moreover, as a patient, how could you not want the person sitting with you in these circumstances to be sympathetic and supportive? How much the timing, content, and intensity of this preparation matter remains open for systematic inquiry. As indicated in Table 1, for the most important studies of psilocybin in major depression, the time devoted to preparation could be as long as 8 hours and as short as 2 hours (9, 12).

On the day of administration, safeguarding requires that there be a responsible person present. It has proved possible to employ a single individual or even a group setting. This is analogous to the requirements for support of other medical procedures, such as cancer chemotherapy, but it is obviously made more complicated by the change in consciousness and the potential for abuse of the patient in an altered state (3). In the COMP 001 trial (13, 14), the therapist was required to remain present and available for support but explicitly to refrain from active guiding or prolonged discussions. If the participant became active or restless, the therapist was to encourage direction of their attention inward. The core principle was to help participants maintain attention on the experience of the present moment and be open to a maximally immersive drug experience.

The data on the impact of integration or debriefing after the psychedelic experience remain scant. Integration was relatively brief in the controlled studies in treatment-resistant depression (two sessions). Furthermore, the dose-related reduction in depressive symptoms was fully developed in responders on the day following treatment (13), and before any integration had taken place. Patients can also describe the emotional breakthroughs achieved by the treatment at this stage. A scale measuring emotional breakthrough (the Emotional Breakthrough Inventory) (15) predicts the reduction in depressive symptom severity several weeks later (16). Thus, there is little room for inference from existing studies of a major effect of integration, the element of the total treatment that most obviously entails patient/therapist interaction of the kind generic to psychotherapies. Usually 2–3 hours is allotted to integration, but sometimes the duration is not clearly specified. The methodology for integration is described as nondirective in most cases and usually is not specified in a manual.

The role of integration, and indeed of additional psychotherapy of other kinds, is, in our opinion, still an open

TABLE 1. The major studies of psilocybin treatment in major depressive disorder (MDD), treatment-resistant depression (TRD), and alcohol use disorder (AUD), and of MDMA for posttraumatic stress disorder (PTSD)

	Imperial College London (12, 35)	Johns Hopkins (32, 36)	Imperial College London (37)	COMPASS Pathways (13, 38)	University of Zurich (39)	NYU (21, 23)	Multidisciplinary Association for Psychedelic Studies (30)
Disorder and N	TRD (N=20)	MDD (N=24)	MDD (N=59)	TRD (N=232)	MDD (N=52)	AUD (N=95)	PTSD (N=90)
Design	Open-label	Randomized	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, active placebo-controlled plus psychotherapy	Randomized, double-blind, active placebo-controlled plus psychotherapy
Dose	Psilocybin: first dose, 10 mg; second dose, 25 mg	Psilocybin: first dose, 20 mg/70 kg; second dose, 30 mg/70 kg	Psilocybin: first and second doses, 25 mg; compared with 6 weeks of daily oral escitalopram	Psilocybin; one dose, either 25 mg or 10 mg	Psilocybin: one dose, 14.98 mg/70 kg (0.215 mg/kg)	Psilocybin: first dose, 25 mg/70 kg; second dose, 25–40 mg/70 kg	MDMA: variable dosing
Preparation	One 4-hour session	8 hours total	One 3-hour session before first administration and a 1-hour telephone session before second administration	Two sessions, ~2 hours total	Two sessions, 2 hours total	Two 4-hour sessions and one 1-hour session	Three sessions, 4.5 hours total
Integration	By telephone the day after low-dose administration; in person the day after the high-dose administration; another visit 1 week after the high-dose administration	2–3 hours total	One session after each administration; three telephone sessions weekly after each administration	~2.5 hours total	3 hours total	Two 2-hour sessions	Nine sessions (three per drug administration), 13.5 hours total
Therapy support	Two clinical psychiatrists	Two therapists	Two therapists	Two therapists	One therapist	Two therapists	Two therapists
Model specified	Nondirective psychological support; no manual specified	Nondirective psychological support; no manual specified	Nondirective psychological support based on the "accept, connect, embody" (ACE) model	Nondirective psychological support; manualized	Psychological counseling; no manual specified	Manualized psychotherapy based on components of addiction treatment	Manualized treatment; strong emphasis on therapist interaction

and very interesting question. It may be important, again from a safety perspective, to assess patients for unusual persistent beliefs or the impulsive intention to make drastic changes in their lives (for example, in their wills or in other major financial decisions). In addition, the experience is so unusual that psychedelically naive patients just want to talk to someone who has seen others in this state before. It is the assumption of many therapists that integration is crucial to efficacy (17). The complexity they see in the process implies much more work than is possible in two integration sessions.

But, alternatively, a more systematic use of behavioral activation or cognitive-behavioral therapy (CBT) in the time immediately after the psychedelic experience might capitalize on the fertile state that hypothetically results from the increase in synaptic plasticity seen in animals and implied by EEG changes in humans (18–20). Indeed, studies that formally seek to determine whether psychedelic treatment augments the efficacy of evidence-based psychotherapy might include trauma-focused CBT or cognitive processing therapy for PTSD. The recent trials of psilocybin for alcohol and

tobacco use disorders (21, 22) wove in CBT/motivational enhancement therapy approaches alongside the psychological support model (23). An automated training intervention was found to extend the efficacy of ketamine (24). These approaches add many additional hours of therapy time (see Table 1 for an example in alcohol use disorder). However, their incremental benefit is currently unclear because of a lack of necessary comparators. Supported by rigorous randomized clinical trials, they offer a glimpse into how psilocybin may fit into conventional evidence-based treatment programs once its efficacy and safety have been confirmed at scale for regulatory approval. They are not comparable with the approach employed so far to *achieve* regulatory approval.

HOW DOES A PSYCHEDELIC EXPERIENCE WORK AS ANTIDEPRESSANT TREATMENT?

Psychedelics facilitate powerful experiences that may drive compelling narratives through emotional breakthrough—this is what psychotherapists often aspire to achieve in a prolonged course of psychotherapy. However, this resemblance does not necessarily imply equivalence or a common mechanism. Even if the psychedelic experience results in a change of cognitive schemas and is the mechanism of recovery, is it sensible to describe this as psychotherapy if it is driven by a psychopharmacological intervention under supportive conditions?

The psychedelic experience is produced most consistently by serotonergic agonists. Its intensity correlates with 5-HT_{2A} receptor occupancy, and it is associated with impressive changes in connectivity between brain areas, as seen with functional MRI both under drug and subsequently (25–27). Persisting effects on brain biochemistry and connectivity have also been described in animals (28). The dose-effect relationship seen in treatment-resistant depression with psilocybin lends itself well to a pharmacological explanation. The details are yet to translate into a definitive theory of drug action because the biological basis of depression remains poorly specified, but the comparative pharmacology of serotonergic agonists and other fast-acting drugs, such as ketamine, is already intriguing (29).

MDMA

The use of 3,4-methylenedioxymethamphetamine (MDMA) for the treatment of PTSD appears intermediate between the psycholytic and psychedelic approaches and has commonly, and correctly, been described as assisting psychotherapy. It entails longer patient-therapist contact over multiple sessions with and without drug (Table 1). It clearly raises multiple concerns about whether the drug effect per se is distinguishable. However, MDMA's effects—notably increased empathy and sociability—should be distinguished from the psychedelic experience (10). The manual used in the recent trials clearly implies significant active interaction between patient and therapist, albeit with an "inner-directed" approach that allows spontaneous material to emerge as a manifestation of drug effect (30). Such interaction between patient and therapist during the MDMA experience has inevitably raised ethical concerns because of the vulnerable state of the patient (2, 31). Undoubtedly it makes sense to speak of a psychotherapy being assisted by a drug if the psychotherapy is itself a stand-alone treatment and it is simply delivered under the influence of the drug.

CONCLUSIONS

High doses of serotonergic agonists produce characteristic changes in states of consciousness by actions on the serotonergic system of the brain. The experience is dose related and largely involuntary. The psychedelic experience requires preparation, informed consent, and support during drug administration for reasons of safety. While the experience appears to be therapeutic for depressed patients, it has not been shown to be a psychotherapy as normally understood. Hence it does not provide "psychedelic-assisted psychotherapy." Indeed, psychedelic states are largely incompatible with the interactions of conventional psychotherapy. To understand the actions of existing and future drugs with psychedelic properties, regulators are likely to prefer psychological support to be focused on safety, not efficacy. In no way does this difference in emphasis diminish the importance of such support for the development of the approach.

The effects of a psychedelic experience on depressive symptoms can be long-lasting (32), and long-lasting effects have been achieved in existing studies without much time being spent on integration of the experience. The role of integration has enjoyed a strong traditional emphasis without systematic study of how much it really matters. Moreover, the nondirective approach has historical resonance but may not be optimal. If the postpsychedelic state is one in which the brain is more plastic (20, 33), there may be scope for innovation in the use of a range of focused psychotherapies, additional conventional antidepressant drugs, or even neurostimulation for specific clinical indications. These additional treatments may eventually be described as psychedelic-*preceded* therapies.

Finally, drug doses matter. Lower doses of serotonergic agonists will be compatible with simultaneous conventional psychotherapy, but the doses may necessarily be subpsychedelic. Will it then be logical to describe the approach as "psychedelic-assisted psychotherapy"? In our view, it will not, unless we choose to use the term "psychedelic drug" as a category. This would be an error of the kind of that led to the naming of drug classes by indication rather than mode of action (34).

In summary, "psychedelic-assisted psychotherapy" does not capture the true mechanism of change facilitated by psychedelic experience. The effects observed thus far in the best controlled studies of psychedelic treatment must be attributed to the drug itself and not to psychotherapy. In the case of psilocybin, for

example, let us say simply "psilocybin treatment." To continue to use the "PAT" phrase at this stage risks confusing and impeding the development of serotonergic agonists as medications at psychedelic doses. We can think more clearly without it.

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