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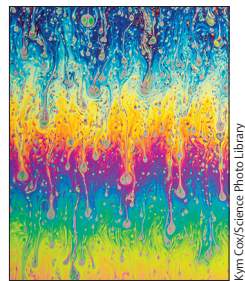
## Psychedelic medicine: safety and ethical concerns

With the current surge of interest in the field of psychedelic research, a psychedelic renaissance in psychiatry depends primarily on the ability to establish safe and ethical settings for the use of these experimental medicines. However, few opportunities exist for learning the safe and effective administration of psychedelic therapies.<sup>1</sup> When psychedelics were embraced by modern medicine in the 1950s and 1960s, enthusiasm and fervent portentousness overtook pragmatism before psychedelic science could develop safe and consistent structures.<sup>2</sup> A similar collective enthusiasm is palpable in psychedelic psychiatry—a field that does not yet have in place the means to manage the consequences of its much-anticipated success. We wish to draw attention to several issues that need to be thoroughly addressed to allow the field of psychedelic research to grow in a safe and sustainable manner.

With the US Food and Drug Administration (FDA) granting breakthrough therapy designations for both 3,4-methylenedioxymethamphetamine (MDMA) (in 2017) and psilocybin (in 2019),<sup>3</sup> and with growing interest from investors and health-care entrepreneurs, many investigators today are excited to examine how psychedelic therapies might address the unmet needs of patients with substance use disorders, treatment-resistant mood disorders, and trauma-related disorders, among others. Heifets and Malenka described the study of psychedelics as “disruptive psychopharmacology”.<sup>4</sup> We agree these compounds have the potential to lead to substantial innovations in therapeutics and neuroscience, but believe they can also be disruptive for other reasons. Classic psychedelics, such as psilocybin and lysergide, and

atypical psychedelics, such as MDMA, have been found to be relatively well tolerated in early-phase clinical trials.<sup>3,5</sup> However, psychedelics can have lingering effects that include increased suggestibility<sup>6</sup> and affective instability, as well as altered ego structure, social behaviour, and philosophical worldview.<sup>2</sup> Stated simply, psychedelics can induce a vulnerable state both during and after treatment sessions. Therefore, to assure the safe and responsible clinical administration of psychedelics, we need to develop and disseminate rigorous ethical and practice standards that are commensurate with the novelty and breadth of the effects that these compounds can have on individuals.

We do not anticipate that eliciting clinically significant effect sizes in primary endpoints will be the key challenge to implementing psychedelic therapy given the current clinical data,<sup>3,5</sup> heightened expectations regarding the so-called transformative effects of these drugs, and the pervasive functional unblinding that is evident across most of these studies. Instead, the more pressing issues affecting the roll out of these therapies will arise from dynamics between providers and patients (eg, the challenges of co-creating truly informed consent, minimising conflicts of interest, and avoiding practising outside the provider's scope of competency). Unfortunately, not only are disruptive responses evident in some people who ingest psychedelics, but occasionally these responses can be found in some individuals who have a strong desire to administer the drugs to others (for the avoidance of doubt, this statement does not refer to any of the people cited in this Comment). Even though treatment providers who have personal experience of taking psychedelics might be better at



anticipating the clinical needs of their patients than those who do not have personal experience, we advise caution when evaluating the judgment of research and clinical colleagues who have only begun to take psychedelics within the past couple of years. Despite the association between psychedelic use and ego dissolution,<sup>7</sup> grandiosity can loom large with initial psychedelic experiences, leading even conservative individuals to become wildly enthusiastic about the potentials of psychedelics to heal and transform. Although this enthusiasm tends to wane over time, the risks of ego inflation and grandiosity can persist in susceptible personality types. Conversely, people who take psychedelics might aggrandise and fetishise the therapists who administer the drugs to them. There are well known baseline risks of parental or erotic transference in conventional psychotherapy.<sup>8</sup> We suggest that the risks of problematic interpersonal dynamics are magnified when a patient's therapist not only administers unconditional acceptance and validation, but also expedites access to experiences of transcendence or profound catharsis via a drug.

We have served as investigators and clinicians on three early-phase clinical trials of psilocybin- assisted or MDMA-assisted psychotherapy, one safety and tolerability study of MDMA in healthy volunteers, and several biomedical and ethnographic investigations of psychedelic use in community settings involving observations of hundreds of individuals consuming psychedelics. With increasing frequency over the years, we have received letters, emails, and phone calls from concerned individuals who are seeking help while recovering from challenging psychedelic experiences, feel harmed by unethical psychedelic providers, or are desperately seeking psychedelic therapy for themselves or a loved one. Psychedelic medicines carry a truly uncanny allure and risk-benefit profile, and regulatory risk evaluation mitigation strategies can have their shortcomings.<sup>9</sup> Hence, our collective challenge as future psychedelic providers is to develop a system of rigorous peer-review and supervision that will allow professionals in the field to more safely navigate the possible, and at times unavoidable, ethically murky undercurrents that might emerge.

We hope to bring transparency to a collection of heuristics that are often whispered about in the

background, which we now feel would be appropriate for psychiatry at large to consider publicly. Researchers and health-care providers have an ethical duty to mitigate the risk of repeating errors in judgment that curtailed early progress in psychedelic science. We encourage investigators and clinicians to contemplate the responsibility that we all have for the conduct of individuals who we train to provide psychedelics, and to seek guidance from institutions that oversee the ethical practice of other health-care providers (eg, anesthesiologists and geriatricians) who work with especially vulnerable populations.<sup>10</sup> For the sake of patient safety and wellbeing, let us fulfil our responsibility to develop and implement elevated standards of clinical training, quality assurance, and peer-review for these wondrously disruptive medicines.

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**Brian T Anderson, Alicia L Danforth, \*Charles S Grob**  
**cgrob@lundquist.org**

Department of Psychiatry, Weill Institute for Neurosciences, University of California, San Francisco, CA, USA (BTA); Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, CA, USA (BTA); and Lundquist Institute (CSG, ALD) and Department of Psychiatry (CSG), Harbor-UCLA Medical Center, Torrance, CA 90509, USA

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