Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA

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4-phosphorloxy-N,N-dimethyltryptamine (psilocybin) and methylenedioxymethamfetamine (MDMA), best known for their illegal use as psychedelic drugs, are showing promise as therapeutics in a resurgence of clinical research during the past 10 years. Psilocybin is being tested for alcoholism, smoking cessation, and in patients with advanced cancer with anxiety. MDMA is showing encouraging results as a treatment for refractory post-traumatic stress disorder, social anxiety in autistic adults, and anxiety associated with a life-threatening illness. Both drugs are studied as adjuncts or catalysts to psychotherapy, rather than as stand-alone drug treatments. This model of drug-assisted psychotherapy is a possible alternative to existing pharmacological and psychological treatments in psychiatry. Further research is needed to fully assess the potential of these compounds in the management of these common disorders that are difficult to treat with existing methods.

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Introduction

Advances in psychopharmacology during the past 60 years have benefited millions of patients with debilitating but common psychiatric disorders. However, approved psychopharmacological drugs have fallen short of definitively correcting underlying pathology and curing psychiatric illness. Antipsychotics, antidepressants, anxiolytics, and mood stabilisers can help to decrease symptoms, and can even be life-saving for some patients; however, for many, the benefits are disappointing, and the side-effects of long-term daily use can be problematic. Advances in evidence-based psychotherapy have yielded improved treatments for several disorders, including post-traumatic stress disorder (PTSD) and anxiety associated with life-threatening illness. Psychological treatments seem to be more effective than medications for PTSD;[1] however, a large percentage of patients do not respond adequately to psychotherapy, with or without concomitant medications.[2,3] Interest is also growing in development of more effective psychotherapy for existential suffering at the end of life.[4] Research into methods to improve psychological treatments is especially important in view of a 2013 meta-analysis[5] reporting that patients' preference for psychotherapy is three times greater than for medication.

In our experience, most clinicians who treat psychiatric patients are all too familiar with the suffering and frustration endured by those who try successive medications, often with several drugs, but do not find relief or cannot tolerate the side-effects. Likewise, patients frequently do not make adequate progress in psychotherapy, or drop out because they are not able to tolerate emotionally challenging aspects of treatment such as prolonged exposure. The need for new approaches to psychological treatments is clear. The limitations of existing pharmacotherapy and psychotherapy and the paucity of resources for psychotherapy research and treatment leave millions of patients suffering, and psychiatrists are faced with what has been called psychiatry's identity crisis.[6]

A promising new model of treatment is under investigation in a resurgence of research into use of psychedelic drugs to augment psychotherapy. In this model, the drug is used on one or a few occasions during psychotherapy sessions to overcome obstacles to successful psychotherapy and to catalyse a therapeutic experience. It is theorised that the experience itself, rather than simply the pharmacological effects of the drug, might lead to cure or sustained remission of severe, treatment-refractory psychiatric disorders. Results of both early and recent studies of 4-phosphorloxy-N,N-dimethyltryptamine (psilocybin) or methylenedioxymethamfetamine (MDMA) in conjunction with psychotherapy offer the possibility of rapid, comprehensive, and lasting psychological healing and growth, and raise many intriguing questions about the mechanisms and clinical applicability of this model of treatment. Therapeutic approaches used in psilocybin and MDMA studies overlap substantially, but the two drugs have been studied for different indications in most cases. Both approaches include inner focus and talking with therapists; however, in MDMA-assisted sessions, periods of talking generally alternate with periods of inner focus, whereas in psilocybin-assisted sessions, most of the talking occurs before and after the period of drug effect. We discuss psilocybin and MDMA separately.

Psilocybin-assisted psychotherapy

The classic hallucinogen psilocybin exists in nature as an active alkaloid in more than 100 species of mushrooms. Although used for healing and divination in many indigenous cultures in South and Central America, psilocybin was not discovered by Western cultures until the 1950s.[7] During the 1950s to early 1970s, together with the better known lysergic acid diethylamide (LSD), psilocybin was used in investigations in human beings. In addition to their range of effects on CNS function, psilocybin and LSD had promising therapeutic potential in preliminary studies, most interestingly in patients with various treatment-refractory disorders. Unfortunately, these studies were brought to an abrupt halt, as a result of the notorious so-called culture wars of that era.[8]

One population in which this novel psychedelic treatment model is showing promising results, and for whom conventional treatments have long been known to be inadequate, are patients with advanced-stage cancer with severe reactive anxiety. Results of a series of studies done several decades ago showed subtantive and sustained reductions in anxiety, improved mood, and enhanced quality of life in patients with terminal cancer after one closely monitored dose of LSD or di-propyltryptamine (DPT), a compound chemically related to psilocybin.[9] More recent investigations have corroborated these early findings, with moderate-dose psilocybin as the active agent for a one-session treatment model (table 1).[10–13]

The first study in more than 30 years to investigate the potential of a classic hallucinogen treatment model in patients with advanced cancer and anxiety, at Harbor-UCLA Medical Center (Torrance, CA, USA) and the Los Angeles BioMedical Research Institute (Torrance, CA, USA) and supported by the Heffter Research Institute (Santa Fe, NM, USA), used a double-blind, placebo-controlled research model.[11] 12 patients functioning as their own controls were given two separate experimental treatment sessions 1 month apart, receiving the active drug, psilocybin, on one occasion and placebo on the other, in a random order. All patients were screened and prepared through several meetings with treatment staff to establish rapport and acquire understanding of the range of altered states of consciousness that they might encounter during their treatment sessions. Follow-up data were collected for 6 months after the second treatment session. Results included safe physiological and psychological responses during treatment sessions. No clinically significant adverse events were noted. Significant reductions in anxiety at 1 month and 3 months after treatment were measured with the State-Trait Anxiety Inventory trait anxiety subscale, and an improvement of mood was measured with the Beck Depression Inventory, which reached significance at 6 months. For this first investigation of use of a classic hallucinogen treatment in several decades, a moderate dose of 0·2 mg/kg bodyweight was used. Subsequently, two other research groups, at Johns Hopkins University (Baltimore, MD, USA) and New York University (New York, NY, USA), have received approval from the US Food and Drug Administration (FDA) to use a higher dose in a similar population of patients. Publication of the results of these larger-scale studies is expected to be forthcoming (Roland Griffiths [Johns Hopkins University School of Medicine, Baltimore, MD, USA] and Stephen Ross [New York University, New York, NY, USA], personal communication). A similar study in Switzerland with LSD rather than psilocybin showed a strong effect size in reduction of state and trait anxiety.[14]

One line of inquiry that has emerged from research done in the 1960s[15] has been the study of the range of profound psychospiritual experiences that might be induced by psychedelic drugs when administered under optimal conditions (set and setting), and their role in achieving therapeutic outcomes.[16,17] The capacity to activate innate mechanisms for psychospiritual healing, especially in individuals with life-threatening medical illness and severe existential anxiety, depression, and demoralisation, might be an important advance for the healing arts and medicine. This shift is taking place in the context of major developments in neurotheology, which are elucidating the biological or brain basis of religious or spiritual experiences.[18]

Results of carefully undertaken studies at Johns Hopkins University showed that screened healthy volunteers treated under optimal conditions with high-dose psilocybin reliably experienced profound mystical experiences (defined as encountering a profound sense of unity, transcendence of time and space, deeply felt positive mood, noetic quality, ineffability, transiency, and paradoxicality) infused with a renewed sense of purpose and meaning, that even more than a year later retained their personal value.[17,19–21] The association between psychedelic-induced mystical experience and therapeutic outcome when psychedelic drugs are given under optimal conditions provides a potentially valuable therapeutic intervention for disorders that are otherwise difficult to treat, including end-of-life anxiety and alcoholism—a very dangerous disorder with high rates of resistance to existing treatments, and the focus of several promising research studies starting in the 1950s and continuing until the early 1970s.[22,23] This strategy has also been studied as part of a potential treatment model at the University of New Mexico (Albuquerque, NM, USA) and New York University. For example, Bogenschutz and colleagues[12] showed that a single dose of psilocybin resulted in reductions in drinking behaviour and craving in ten individuals with alcohol use disorder. In a pilot

	Location	Status	Sample size	Timing
Obsessive-compulsive disorder[10]	University of Arizona (Tucson, AZ, USA)	Complete	9	Results published in 2006
Cancer anxiety[11]	Harbor–UCLA Medical Center (Torrance, CA, USA)	Complete	12	Results published in 2011
Cancer anxiety (ClinicalTrials.gov, number NCT00465595)	Johns Hopkins University (Baltimore, MD, USA)	Complete	51	Results submitted for publication
Cancer anxiety (ClinicalTrials.gov, number NCT00957359)	New York University (New York, NY, USA)	Complete	31	Results submitted for publication
Alcohol dependence[12]	University of New Mexico (Albuquerque, NM, USA)	Complete	10	Results published in 2015
Alcohol dependence (ClinicalTrials.gov, number NCT02061293)	New York University (New York, NY, USA)	Ongoing	180	Expected completion 2016
Tobacco cigarette addiction[13]	Johns Hopkins University (Baltimore, MD, USA)	Complete	15	Results published in 2014
Cocaine use (ClinicalTrials.gov, number NCT02037126)	University of Alabama (Tuscaloosa, AL, USA)	Ongoing	40	Estimated completion May, 2017

Psilocybin=4-phosphorloxy-N,N-dimethyltryptamine.

Table 1: **Phase 2 studies of psilocybin-assisted psychotherapy**

study, Johnson and colleagues[13] reported a substantially increased smoking cessation rate and improvement in biomarkers assessing smoking status after psilocybin treatment. 12 (80%) of 15 participants showed 7-day point prevalence abstinence in self-report measures of smoking behaviour at 6-month follow-up. If replicated in large and rigorous future studies, such impressive results would have enormous public health implications, in view of the high mortality associated with tobacco, which is several times higher than that of all other drugs of abuse combined, including alcohol.

The neuropsychopharmacological mechanisms of action of psilocybin and other similar psychedelic drugs are thought to be mediated via fairly specific binding to serotonergic 5-HT_2 receptors, primarily 5-HT_{2A} receptors, although non-5-HT_2 receptors are probably also involved.[24,25] Downregulation of 5-HT_{2A} receptors mediates antidepressant and antianxiety effects of antidepressants and atypical antipsychotics.[26] Because of the high binding affinity of psilocybin and other psychedelic drugs to the 5-HT_{2A} receptor, it might produce its effects in human beings mostly, but not wholly, through modulation of 5-HT_{2A} receptors, in addition to complex downstream second messenger signalling and gene-expression effects.[27,28]

In view of the long-standing Western cultural reputation of psychedelic drugs as dangerous drugs of abuse, when taken recreationally by vulnerable individuals under uncontrolled and high-risk conditions, to establish and maintain strong safety parameters is essential when undertaking modern, approved research into the therapeutic potential of psychedelic drugs. Careful investigation of the extensive psychiatric research record with psychedelic drugs from the 1950s to early 1970s identified an extremely small number of adverse outcomes in formal research studies.[29,30] An important contribution by the Johns Hopkins psilocybin research group is a set of safety guidelines for clinical research with hallucinogens,[31] which should be used as standard in this rapidly changing field. Careful screening and monitoring, specifically for underlying psychological and cardiovascular vulnerabilities, substantially reduce risks incurred by unwitting recreational users.

MDMA-assisted psychotherapy

MDMA has become infamous for its use as the purported ingredient in recreational ecstasy, although results of surveys have shown that drugs other than MDMA were present in a high proportion of collected samples.[32–34] Less well known is that in the late 1970s and early 1980s, before MDMA became an illegal Schedule 1 compound, it was used in conjunction with psychotherapy by an estimated 4000 psychiatrists and psychologists.[35] MDMA has been called an entactogen, meaning literally "to produce touching within", referring to its tendency to enhance inner awareness and distinguishing it from classic psychedelic drugs such as psilocybin.[36,37] Case reports of successful clinical use were published, but no controlled research was done at that time.[38,39] Descriptions of the therapeutic process catalysed by MDMA suggested that it might be especially useful for treatment of PTSD. For example, Greer and Tolbert[39] stated that, "clients found it comfortable to be aware of, to communicate, and to remember thoughts and feelings that are usually accompanied by fear and anxiety".

Because of the urgent public health need for a wider range of effective PTSD treatments, these promising reports should have quickly led to formal investigations of the potential risks and benefits of MDMA as a therapeutic agent. Unfortunately, a hostile regulatory and funding climate inhibited research of MDMA treatment for nearly 20 years. Meanwhile, a large amount of money has been spent worldwide on preclinical research, retrospective studies in recreational ecstasy users, and a few phase 1 trials in healthy volunteers assessing the risks of MDMA without investigation of the possible benefits. From the mid-1980s to early 2000s, substantial US National Institutes of Health (NIH) investment was made to investigate serotonin and dopamine neurotoxicity induced by MDMA, in animals and human beings, although careful inspection of many of these studies identified flaws in the methods.[40–42] Fortunately, now that the benefits as well as the risks are being studied with rigorous research designs, existing preclinical and retrospective data are available to the non-profit research sponsors who have taken up the effort. As a result, far more is known about the range of effects and the risks of MDMA, which has been taken by millions of people worldwide, than about usual investigational new drugs.

A comprehensive discussion of MDMA toxicity is beyond the scope of this Personal View, and possible neurotoxic effects in recreational users are still under debate. When used in high-risk contexts, MDMA can be dangerous, and rarely recreational users have died, usually of heat stroke and dehydration during raves or of brain oedema from over-hydration in an ill-informed attempt to avoid dehydration. A specific area of concern regarding possible MDMA toxicity comes from studies of recreational users, some of whom performed more poorly on memory tests than did controls who did not use drugs.[43] Almost all studies in this population have been retrospective, and are fraught with problems with methods, such as polydrug use and uncertainty about the composition of drugs taken.[44–46] The study best designed to minimise these confounders identified "little evidence of decreased cognitive performance in ecstasy users, save for poorer strategic self-regulation… [that] might have reflected a pre-morbid attribute of ecstasy users".[47] This subject has been debated at length in the medical literature, and the most evidence supports continued investigation of the therapeutic benefits of MDMA (reviewed by Doblin and colleagues).[48] Many approved and clinically useful psychiatric medications are well known to have dose-dependent and frequency-dependent neurotoxic effects. The risks of these drugs are

often judged to be acceptable compared with the untreated disease state in question. MDMA and psilocybin have the advantage of being given only once or a few times rather than daily for months or years.

What is most relevant to risk/benefit calculations for clinical research and possible clinical use is evidence that pure MDMA in moderate doses can be given safely to individuals participating in clinical trials in controlled medical settings. More than 1100 individuals have received MDMA in phase 1 or phase 2 clinical trials so far without any unexpected drug-related serious adverse events. The only drug-related serious adverse event reported was a transient increase in pre-existing ventricular ectopy requiring overnight observation; there was no associated cardiac disease identified on further cardiac work-up. A phase 2 study in patients with PTSD that included neuropsychological testing before and after two doses of MDMA or inactive placebo reported no evidence of impairment.[49]

So far, two phase 2 clinical trials[49–51] testing MDMA-assisted psychotherapy for treatment-resistant PTSD have been completed. In view of their encouraging results, these double-blind, placebo-controlled trials support the hypothesis that MDMA, used as a catalyst to psychotherapy, can be effective in treatment of PTSD in patients who did not respond to previous psychotherapy or medications. Similar additional trials are underway in the USA, (ClinicalTrials.gov, numbers NCT01458327, NCT01211405, and NCT01793610), Canada (ClinicalTrials.gov, number NCT01958593), and Israel (ClinicalTrials.gov, number NCT01689740). An earlier phase 2 dose-escalation trial started in Spain in 2000, but was terminated because pressure from the Madrid Anti-Drug Authority led to permission to use the study site being revoked. No medical or scientific reasons existed for termination of the study.[52]

In the first completed phase 2 trial, in 20 patients who had not responded to both psychotherapy and pharmacotherapy (with average duration of PTSD of >20 years), participants randomly assigned to MDMA with psychotherapy had significantly greater decreases in PTSD symptoms than did participants assigned to receive inactive placebo with the same psychotherapy, and 83% no longer met criteria for PTSD, compared with 25% of placebo participants.[49] When seven of the eight patients in the placebo group subsequently received MDMA-assisted psychotherapy in an open-label crossover group, they all achieved roughly the same level of improvement as the original MDMA group. A long-term follow-up study a mean of 45·4 months (range 17–74, SD 17·3) later reported that at least 74% had durable remission of PTSD symptoms.[50] A similar study in Switzerland with 12 patients did not reach statistical significance in Clinician Administered PTSD Scale score reductions, but nevertheless did have a strong effect size of more than 1, and showed significant reductions in the Posttraumatic Diagnostic Scale.[51,53]

The success of MDMA-assisted psychotherapy in these studies was not simply due to replacing one form of psychotherapy with another, or one drug with a more effective drug; rather it is an altogether different approach that could apply to various psychoactive compounds. This approach involves use of a drug to support and catalyse a more effective therapeutic process by stimulating access to an individual's innate ability to engage in his or her own unique course of healing. Participants in these clinical trials, in addition to showing improvements in validated measures of PTSD symptoms, often report deeply meaningful therapeutic experiences and ensuing improvements in various areas of their lives. On long-term follow-up questionnaires, most participants endorsed benefits such as "increased self-awareness and understanding" and "enhanced spiritual life".[50] These responses suggest a subjectively authentic process of psychological and spiritual exploration and growth that could logically be expected to enable trauma processing and symptom reduction, and to promote healthy psychological development.

These results are based not on daily medication doses, but on two or three doses of MDMA, spaced several weeks apart, during 8-h psychotherapy sessions in which periods of inner focus are as important as periods of interaction with the therapists. Furthermore, the therapeutic process is not limited to the period of drug effect (MDMA has a half-life of about 8 h),[54] but continues over time.[50] Accordingly, MDMA research protocols include follow-up non-drug psychotherapy sessions to support the ongoing lessons and challenges of integrating the resulting psychological changes into daily life.

The mechanism of action of MDMA as a catalyst to psychotherapy is the subject of ongoing research, so our observations about it are speculative. During MDMA-assisted psychotherapy sessions, we observe a decrease in avoidance and defensiveness accompanied by clearer memory of past events, and willingness and ability to process them. Additionally, MDMA research participants often show a new awareness of their own counterproductive patterns of emotional and cognitive response to trauma, and a capacity for fearless and compassionate reappraisal—in many ways the ideal effects to augment psychotherapy. MDMA does not make revisiting traumatic memories easy, and certainly not ecstatic, but it can make it possible for individuals who had not been able to process trauma effectively during months or years of psychotherapy. This effect can be conceptualised in various ways: that the prosocial effects of MDMA might improve the therapeutic alliance with patients who have difficulty trusting; that MDMA in a therapeutic set and setting provides several hours in the optimal arousal zone, during which therapeutic change is possible;[55] that MDMA enables memory retrieval and reconsolidation with new associations to safety; or that MDMA causes a shift from constrained styles of thinking to less rigid, unrestrained thinking.[56] Each of these concepts is consistent with what is known about the physiological

effects of MDMA, which include: release and reuptake inhibition of serotonin, and to a lesser extent dopamine and norepinephrine; release of oxytocin and prolactin; decreased activity in amygdala and hippocampus,[56] and perhaps increased activity in medial prefrontal cortex;[57] increase in resting state functional connectivity (RSFC) between amygdala and hippocampus; and decreased RSFC between ventromedial prefrontal cortex and posterior cingulate cortex.[56] Additionally, healthy volunteers given MDMA have reported a less negative response to worst autobiographical memories, and fMRI data showed attenuated activation to worst memories in the left anterior temporal cortex.[58] Several studies are underway to further elucidate MDMA's therapeutic mechanisms. A substudy of MP-8 (table 2) has examined fMRI with trauma script exposure before and after MDMA-assisted psychotherapy (results pending; ClinicalTrials.gov, number NCT02102802), and another study of individuals with PTSD examining fMRI with trauma script exposure during peak MDMA effects is planned at Cardiff University (Ben Sessa, Imperial College London, London, UK, and Cardiff University, Cardiff, Wales, UK, personal communication).

An additional group of patients in whom an MDMA treatment model is being investigated are adults on the autistic spectrum with social anxiety. An ongoing FDA-approved double-blind, placebo-controlled study (ClinicalTrials.gov, number NCT02008396) is using two closely monitored sessions of moderate-dose MDMA in a screened population naive to the drug.[59] Although outcome data are masked until the conclusion of the study, physiological and psychological safety have thus far been carefully monitored and maintained. In addition to clinical outcomes, primarily social anxiety, the study is also assessing the roles of the neurohormones oxytocin and vasopressin, which have been reported to be sensitive to MDMA and have a role in interpersonal connections and bonding.[60]

Relation to other methods of psychotherapy

MDMA-assisted psychotherapy and psilocybin-assisted psychotherapy clearly differ in many ways from most established methods of psychotherapy. The structure, including 8-h psychotherapy sessions, is unusual, and therapists take a fairly non-directive approach. However, to think that what happens in MDMA-assisted sessions would be unfamiliar to therapists experienced in other methods, or that MDMA might be incompatible with various existing therapies, would be a mistake. MDMA-assisted sessions often include imaginal exposure, correction of cognitive distortions, insights about psychodynamics and transference, and other recognisable therapeutic elements. In MDMA-assisted sessions, these elements often occur spontaneously with little or no direction from therapists. The therapeutic method used in MDMA studies is described in detail in our Treatment Manual,[61] and overlap with other therapies has previously been discussed.[62]

	Location	Status	Sample size	Timing
MP-1; treatment-resistant PTSD[51]	South Carolina	Complete	20	Results published 2010
MP-2; treatment-resistant PTSD[53]	Switzerland	Complete	12	Results published 2012
MP-8; veterans, firefighters, police officers with PTSD (ClinicalTrials.gov, number NCT01211405)	South Carolina	Ongoing; treatment complete	24	Expected completion 2016
MP-12; treatment-resistant PTSD (ClinicalTrials.gov, number NCT01793610)	Colorado	Ongoing	23	Expected completion 2016
MP-4; treatment-resistant PTSD (ClinicalTrials.gov, number NCT01958593)	Vancouver	Ongoing	6	Expected completion 2016
MP-9; treatment-resistant PTSD (ClinicalTrials.gov, number NCT01689740)	Beer Ya'akov Mental Hospital, Israel	Ongoing	9	Expected completion 2016
MAA-1; social anxiety in autistic adults (ClinicalTrials.gov, number NCT02008396)	Harbor–UCLA Medical Center (Torrance, CA, USA)	Ongoing	12	Expected completion 2016
MDA-1; MDMA-assisted psychotherapy for anxiety associated with life-threatening illness (ClinicalTrials.gov, number NCT02427568)	California	Ongoing	18	Expected completion 2016

MDMA=methylenedioxymethamfetamine. PTSD=post-traumatic stress disorder.

Table 2: **Phase 2 studies of MDMA-assisted psychotherapy**

Challenges related to masking

The prominent subjective and objective effects of MDMA and psilocybin make masking of investigators and research participants more difficult than it is in studies of many other classes of drugs. Attempts to address this problem by use of low doses of MDMA as an active placebo have had little success (ClinicalTrials.gov, numbers NCT01211405, NCT01793610). Use of other active placebos has been an important aspect of research methods in most recent psilocybin studies. Some of the psilocybin pilot treatment studies were open label,[12] whereas others have used various active placebos.[10,11,19,20] Effective masking of independent raters has been much easier to accomplish, and could be strengthened further in phase 3 trials by randomly assigning each assessment to a blinded rater from a centralised pool.

Summary

In order for medical interventions to be based on valid science, clinical trials should be rigorously designed and undertaken. It is also essential that pursuit of research into promising potential treatments is neither neglected nor blocked by outside forces. In our view, psychedelic research should be pursued as expeditiously as possible. When people are suffering and medicine does not have an adequate response, many will seek alternative treatments. Ideally, patients should be able to go to their physicians for scientifically based guidance and access to the most effective treatments; however, many patients

Panel: Priorities for the next 5 years of MDMA and psilocybin research

- Completion of ongoing phase 2 trials
- Phase 3 trials of safety and efficacy for specific indications (post-traumatic stress disorder, anxiety associated with cancer or severe medical illness, addictions)
- Strengthening of masking of independent outcome raters by use of centralised pools of raters for phase 3 trials
- Expanded research into neuropsychopharmacological mechanisms of action
- Qualitative research into phenomenology of therapeutic experiences in MDMA-assisted or psilocybin-assisted psychotherapy
- Investigation of MDMA in conjunction with various methods of psychotherapy, including established methods

Search strategy and selection criteria

Most of the references cited were known to the authors either because they were included in the Investigators Brochure for the author's Investigational New Drug research, were written by the authors, or were read in preparation for the American Psychiatric Association Symposium on which this manuscript is based. Any additional searches were done with PubMed or Google Scholar. These searches were not planned and were done when necessary to answer a specific question.

will prove unwilling to wait indefinitely for this. If we as a profession are not sufficiently proactive in studying and discovering a range of new treatments, patients will look elsewhere, and will be vulnerable to unproven treatments from unregulated practitioners. Choices about which potential treatments receive research approval and funding should be driven by evidence and patients' needs. Many people do not trust mainstream medicine to advocate their best interests.[63] Sadly, in view of the political and financial forces that have affected medical research in the past few decades, their fears are not wholly unfounded. We should acknowledge this reality, and keenly strive for the academic freedom and funding necessary to investigate potential benefits of psychedelic-assisted psychological treatments. Future studies should expand efforts to establish efficacy and safety in patient populations, to identify which patient populations might be most appropriate to treat, which of these compounds should be used, and to elucidate the neuropsychopharmacological mechanisms of action of MDMA, psilocybin, and other psychedelic drugs (panel). Because recent studies have yielded thousands of hours of video recordings, there is also a rich opportunity to study the phenomenology of MDMA and psilocybin-assisted therapeutic experiences through qualitative research.

Contributors
All authors contributed equally to this manuscript.

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References

1 Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry* 2013; **74:** e541–50.
2 March J, Silva S, Petrycki S, et al, and the Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; **292:** 807–20.
3 Rothbaum BO, Cahill SP, Foa EB, et al. Augmentation of sertraline with prolonged exposure in the treatment of posttraumatic stress disorder. *J Trauma Stress* 2006; **19:** 625–38.
4 LeMay K, Wilson KG. Treatment of existential distress in life threatening illness: a review of manualized interventions. *Clin Psychol Rev* 2008; **28:** 472–93.
5 McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *J Clin Psychiatry* 2013; **74:** 595–602.
6 Friedman RA. Psychiatry's identity crisis.*New York Times* (New York) 2015: http://www.nytimes.com/2015/07/19/opinion/psychiatrys-identity-crisis.html?smprod=nytcore-ipad&smid=nytcore-ipad-share (accessed Sept 27, 2015)
7 Wasson V, Wasson RG. Mushrooms, Russia and History. New York: Pantheon Books, 1957.
8 Grob CS. The politics of ecstasy. *J Psychoactive Drugs* 2002; **34:** 143–44.
9 Grof S, Goodman LE, Richards WA, Kurland AA. LSD-assisted psychotherapy in patients with terminal cancer. *Int Pharmacopsychiatry* 1973; **8:** 129–44.
10 Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J Clin Psychiatry* 2006; **67:** 1735–40.
11 Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry* 2011; **68:** 71–78.
12 Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol* 2015; **29:** 289–99.
13 Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol* 2014; **28:** 983–92.
14 Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *J Nerv Ment Dis* 2014; **202:** 513–20.
15 Pahnke WN. Psychedelic drugs and mystical experience. *Int Psychiatry Clin* 1969; **5:** 149–62.
16 Griffths RR, Grob CS. Hallucinogens as medicine. *Sci Am* 2010; **303:** 76–79.
17 Grob CS, Bossis AP, Griffiths RR. Use of the classic hallucinogen psilocybin for treatment of existential distress associated with cancer. Carr BI, Steel J, eds. Psychological aspects of cancer. New York: Springer, 2013: 291–308.
18 Newberg AB. The Principles of Neurotheology. Burlington: Ashgate Publishing, 2010.

19 Griffiths R, Richards W, Johnson M, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol* 2008; **22:** 621–32.

20 Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl)* 2006; **187:** 268–83.

21 Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology (Berl)* 2011; **218:** 649–65.

22 Grinspoon L, Bakalar JB. Psychedelic drugs reconsidered. New York: Basic Books, 1979.

23 Grob C. MDMA research: preliminary investigations with human subjects. *Int J Drug Policy* 1998; **9:** 119–24.

24 Halberstadt AL, Geyer MA. Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. *Neuropharmacology* 2011; **61:** 364–81.

25 Tylš F, Páleníček T, Horáček J. Psilocybin—summary of knowledge and new perspectives. *Eur Neuropsychopharmacol* 2014; **24:** 342–56.

26 Van Oekelen D, Luyten WH, Leysen JE. 5-HT2A and 5-HT2C receptors and their atypical regulation properties. *Life Sci* 2003; **72:** 2429–49.

27 González-Maeso J, Weisstaub NV, Zhou M, et al. Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* 2007; **53:** 439–52.

28 Nichols CD, Sanders-Bush E. Molecular genetic responses to lysergic acid diethylamide include transcriptional activation of MAP kinase phosphatase-1, C/EBP-beta and ILAD-1, a novel gene with homology to arrestins. *J Neurochem* 2004; **90:** 576–84.

29 Cohen S. Lysergic acid diethylamide: side effects and complications. *J Nerv Ment Dis* 1960; **130:** 30–40.

30 Strassman RJ. Adverse reactions to psychedelic drugs. A review of the literature. *J Nerv Ment Dis* 1984; **172:** 577–95.

31 Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J Psychopharmacol* 2008; **22:** 603–20.

32 Brunt TM, Koeter MW, Niesink RJ, van den Brink W. Linking the pharmacological content of ecstasy tablets to the subjective experiences of drug users. *Psychopharmacology (Berl)* 2012; **220:** 751–62.

33 Tanner-Smith EE. Pharmacological content of tablets sold as "ecstasy": results from an online testing service. *Drug Alcohol Depend* 2006; **83:** 247–54.

34 Baggott M, Heifets B, Jones RT, Mendelson J, Sferios E, Zehnder J. Chemical analysis of ecstasy pills. *JAMA* 2000; **284:** 2190.

35 Holland J. Ecstasy: the complete guide. Holland J, editor. Rochester: Inner Traditions, 2001.

36 Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. *J Psychoactive Drugs* 1986; **18:** 305–13.

37 Nichols DE, Oberlender R. Structure-activity relationships of MDMA and related compounds: a new class of psychoactive drugs? *Ann NY Acad Sci* 1990; **600:** 613–23.

38 Adamson S. Through the gateway of the heart: accounts of experiences with MDMA and other empathogenic substances. San Francisco CA: Four Trees Publications, 1985.

39 Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs* 1998; **30:** 371–79.

40 Grob CS. Deconstructing ecstasy: the politics of MDMA research. *Addict Res Theory* 2000; **8:** 549–88.

41 Grob CS, Poland RE. MDMA. In: Lowinson J H, Ruiz P, Millman RB, Langrod JG, eds. Substance abuse: a comprehensive textbook. 4th edn. Philadelphia, PA: Williams and Wilkins, 2005: 274–86.

42 LeVay S. When Science Goes Wrong. Penguin, 2008.

43 Rogers G, Elston J, Garside R, et al. The harmful health effects of recreational ecstasy: a systematic review of observational evidence. Health Technol Assess 2009; **13:** 1–315.

44 Gouzoulis-Mayfrank E, Daumann J. The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. *J Psychopharmacol* 2006; **20:** 188–93.

45 Cole JC. MDMA and the "ecstasy paradigm". *J Psychoactive Drugs* 2014; **46:** 44–56.

46 Krebs TS, Johansen PO. Methodological weaknesses in non-randomized studies of ecstasy (MDMA) use: a cautionary note to readers and reviewers. *Neuropsychopharmacology* 2012; **37:** 1070–71.

47 Halpern JH, Sherwood AR, Hudson JI, Gruber S, Kozin D, Pope HG Jr. Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs. *Addiction* 2011; **106:** 777–86.

48 Doblin R, Greer G, Holland J, Jerome L, Mithoefer MC, Sessa B. A reconsideration and response to Parrott AC (2013) "Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research". *Hum Psychopharmacol* 2014; **29:** 105–08.

49 Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of +/-3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol* 2011; **25:** 439–52.

50 Mithoefer MC, Wagner MT, Mithoefer AT, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *J Psychopharmacol* 2013; **27:** 28–39.

51 Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (±3,4-methylenedioxy-methamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *J Psychopharmacol* 2013; **27:** 40–52.

52 Bouso JC, Doblin R, Farré M, Alcázar MA, Gómez-Jarabo G. MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. *J Psychoactive Drugs* 2008; **40:** 225–36.

53 Chabrol H, Oehen P. MDMA assisted psychotherapy found to have a large effect for chronic post-traumatic stress disorder. *J Psychopharmacol* 2013; **27:** 865–66.

54 de la Torre R, Farré M, Roset PN, et al. Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. *Ther Drug Monit* 2004; **26:** 137–44.

55 Ogden P, Minton K, Pain C. Trauma and the body: a sensorimotor approach to psychotherapy. Norton series on interpersonal neurobiology. New York: WW Norton & Company, 2006.

56 Carhart-Harris RL, Murphy K, Leech R, et al. The effects of acutely administered 3,4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. *Biol Psychiatry* 2015; **78:** 554–62.

57 Gamma A, Buck A, Berthold T, Liechti ME, Vollenweider FX. 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans. *Neuropsychopharmacology* 2000; **23:** 388–95.

58 Carhart-Harris RL, Wall MB, Erritzoe D, et al. The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *Int J Neuropsychopharmacol* 2014; **17:** 527–40.

59 Danforth AL, Struble CM, Yazar-Klosinski B, Grob CS. MDMA-assisted therapy: a new treatment model for social anxiety in autistic adults. *Prog Neuropsychopharmacol Biol Psychiatry* 2015; **4:** 237–49.

60 Dumont GJ, Sweep FC, van der Steen R, et al. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci* 2009; **4:** 359–66.

61 Mithoefer M. A manual for MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder, version 7. http://www.maps.org/research/mdma/mdma-research-timeline/4887-a-manual-for-mdma-assisted-psychotherapy-in-the-treatment-of-ptsd2015 (accessed Feb 28, 2016).

62 Mithoefer M. MDMA-assisted psychotherapy: how different is it from other psychotherapy? *MAPS Bulletin* 2013; **23:** 10–14.

63 Blendon RJ, Benson JM, Hero JO. Public trust in physicians—U.S. medicine in international perspective. *N Engl J Med* 2014; **371:** 1570–72.