

## COMMENTARY

# Psychedelic Drugs as Therapeutics: No Illusions About the Challenges

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**Interest in the potential therapeutic benefits of psychedelic agents has recently increased. In addition to psilocybin, a wide variety of agents with psychedelic properties have been proposed and partially tested. However, the challenges of obtaining approval to market a restricted psychotomimetic agent are formidable.**

Recent clinical trials with psilocybin for intractable anxiety and depression in patients with life-threatening cancer, a Review article and Commentary in this journal, have renewed interest in the potential therapeutic usefulness of psychedelic agents.<sup>1–5</sup> Medically, in addition to psilocybin, other substances with psychedelic properties, e.g., ketamine, 3,4-methylenedioxymethamphetamine (MDMA), microdoses of lysergic acid diethylamide (LSD), and N, N-dimethyltryptamine (DMT), have been proposed to treat psychiatric and other diseases. While most past hallucinogen research was entirely descriptive, attempts at improved exploratory studies (e.g., obsessive-compulsive disorder, major depression, substance use disorders) have occurred in the past 20 years. While introducing elements of randomization, blinding, and a control arm, these are generally not placebo-controlled studies. Research to understand the mechanism of action of psychedelic agents as neurochemical probes is of scientific interest. The possibility of resetting even part of the brain's default

network would have wide scientific, medical, ethical, and social implications.<sup>4</sup> The obstacles to drug approval remain daunting. This Commentary addresses some of the regulatory considerations and potential precedents.

## PRACTICAL BARRIERS

Pragmatic barriers include: lack of intellectual property protection for composition of matter for old drugs; development costs in the hundreds of millions of dollars; difficulty of designing and conducting double-blind trials with drugs that have easily detected effects; unique clinical trial constraints (e.g., limited appropriate treatment settings, small number of experienced investigators); need for a site license to possess a controlled substance; and the perceived risk of such a product from a pharmaceutical company perspective. In addition, since for most potential therapeutic applications a variety of effective drugs exist, it is not obvious where drugs with a risk of behavioral toxicity would fit.

## PHARMACOLOGY AND MECHANISM OF ACTION

Psychedelic drugs are not identical in their mechanisms of action. Their basic pharmacology is diverse and pleomorphic, including complex agonist and partial agonist/antagonist actions on 5HT<sub>2A</sub>, 5HT<sub>2C</sub>, 5HT<sub>1A</sub>, dopamine D<sub>2</sub>, trace amine associate receptors 1, various transporters (e.g., serotonergic, dopaminergic), intracellular messengers, effects on gene expression, and epigenetic regulators. Such a wide range of pharmacologic mechanisms and targets raises the probability of off-target toxicity and a high risk of interactions with concurrent diseases and drugs.

For the most part, a mechanism of action underlying the putative therapeutic effect is not known for any psychedelic. Drugs are often approved with uncertain mechanisms of action; however, dose-response relationships, duration of action, and toxicity must be well understood and efficacy and safety demonstrated. The two recent trials of psilocybin do not provide information of this type.<sup>2,3</sup> The trial design of investigational drugs combined with structured psychotherapy is well accepted. That said, the intensity of the psychosocial and support component for these studies may have confounded the drug contribution to the observed outcomes.

## PRINCIPLES OF DRUG DEVELOPMENT Study requirements

The fundamental requirements for a new drug product include a defined target disease or symptoms, description and understanding of the disease and its natural history, its pathophysiology, as well as of the new drug's proposed mechanism of action. Clinical trials must be conducted that incorporate reliable endpoints and outcome assessments, and provide evidence of safety and effectiveness. Drug chemical

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**Table 1 Comparison of FDA’s Expedited Programs for Serious Conditions (from FDA Guidance<sup>a</sup>)**

Nature of program	Fast track Designation	Breakthrough therapy Designation	Accelerated approval Approval pathway	Priority review Designation
Qualifying criteria	A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR A drug that has been designated as a qualified infectious disease product	A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness

<sup>a</sup><https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

composition and manufacturing must meet regulatory standards.

Requirements under the US Food and Drug Administration (FDA) IND (Investigational New Drug) regulations include: standard nonclinical toxicology as well as pharmacokinetic studies in animals and humans, phase II studies defining the appropriate patient population, target indication, and dose finding, as well as adequate controlled, phase III clinical trials. Several of the psychedelic clinical trials conducted to date could be viewed as phase II exploratory or hypothesis-testing studies. Clinical studies (phase III efficacy and safety) to fully comply with regulatory standards have yet to be conducted.

These requirements apply equally to high-risk drug products with known toxicity (e.g. thalidomide, isotretinoin, gamma hydroxy-butyrate (GHB) and other drugs controlled under the United States Controlled Substance Act (CSA)). This is particularly true for substances controlled in Schedule I of the CSA. Schedule I drugs (i.e., substances with the highest potential for abuse and no known medical use) include psychotomimetic or hallucinogenic substances such as LSD, psilocybin, cannabis, and cannabis constituents.<sup>6</sup> These drugs are also controlled internationally in Schedule I of the Convention on Psychoactive Substances of 1971.<sup>7</sup>

**Approval of a CSA Schedule I drug**

Precedent exists for the development and approval of CSA Schedule I substances, transforming them into approved albeit controlled drugs. When it has occurred, clinical trials and ultimate approval were for serious and/or unmet medical needs. One example is Marinol, (dronabinol or synthetic Delta-9-THC in an oily capsule formulation), approved for AIDS-related anorexia as an orphan drug in 1985 during the initial phase of the AIDS crisis. At the time of approval, Marinol was placed in CSA Schedule II. Marinol was subsequently approved for cancer chemotherapy-related nausea and vomiting and rescheduled as CSA Schedule III based on postmarketing data in 1999.

GHB is an example of a high-risk sedative drug of abuse, controlled in Schedule I, that was approved as the CSA schedule III drug product, Xyrem. GHB was available as an unscheduled substance for many years prior to its scheduling and approval for cataplexy associated with narcolepsy in 2004.

The cannabis-derived medication Sativex (a mixture of THC and cannabidiol (CBD)) is approved in Canada and Europe for spasticity and is under development for other indications in the US. CBD is under orphan drug development for refractory pediatric epilepsy

syndromes. While public attitudes and state laws have changed with respect to cannabis and its derivatives, CBD remains Schedule I under the CSA and the trials are conducted with full C-I controls.

While the recent publications suggest that psilocybin can be safely administered in a highly controlled clinical trial setting, this does not change the high risk posed by a psychedelic drug used in less controlled, supervised settings, in less carefully selected patients, or if the dose were not controlled. Psychedelic drugs are under strict international control due to the high risk of psychosis and other neuropsychiatric effects, not as much for dependence potential.<sup>8</sup>

**MIGHT SPECIAL FDA REGULATORY PATHWAYS APPLY?**

The FDA provides several programs to facilitate new drug development for unmet or under-met medical needs (Table 1). It is conceivable that a psychedelic drug could be accepted with an IND application for a clinical target with significant unmet need. FDA designations such as Orphan Drug or Fast Track may facilitate development by engaging FDA advice and resources in the development process and potentially expedite FDA review

As the FDA states:

Determining whether a condition is serious is a matter of judgment, but generally is based on whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one. AIDS, Alzheimer's, heart failure, and cancer are obvious examples of serious conditions. However, diseases such as epilepsy, depression, and diabetes are also considered to be serious conditions.

Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy which may be potentially better than available therapy.<sup>9</sup>

Although special pathways appeal, since they suggest faster review, increased interaction with the FDA, reduced trial sizes, and potential market exclusivity, the data requirements remain unchanged. As the FDA makes clear in its Rare Disease Guidance, "the statutory requirement for marketing approval, 'substantial evidence,' based upon adequate and well-controlled studies that are designed and conducted according to principles of Good Clinical Practices (GCP), able to distinguish the effect of a drug from other influences such as 'spontaneous change in the course of a disease, placebo effect or biased observation.'" This requirement is the same for common and rare diseases and conditions that are "an unmet medical need." Conducting such trials with psychedelics will not be straightforward.

#### POSTMARKET RISK EVALUATION AND RISK MITIGATION (REMS)

Any approval of a Schedule I hallucinogenic drug such as psilocybin would likely include a comprehensive REMS with elements to assure safe use, such as the REMS for Xyrem (GHB). Xyrem may be a particularly instructive model in that the GHB substance is controlled under the DEA's CSA Schedule I, while the approved drug product, Xyrem, is controlled in C III under a restrictive REMS. This "bifurcated" scheduling and attendant penalties for misuse/abuse is rare. The REMS for Xyrem includes mandatory patient and prescriber enrollment in a closed system, with restricted dispensing through a central pharmacy, as well as patient and physician education.

If a psychotomimetic drug were to be approved, a comprehensive REMS including restricted use to enroll trained physicians in a certified healthcare setting may be required. Adasuve (loxapine inhalation powder, approved for the acute treatment of agitation), although not a controlled drug, is an example of a high-risk product restricted to use in a certified setting, specifically an enrolled, certified Emergency Department or institution where potentially life-threatening bronchospasm can be treated. A comprehensive REMS would likely be required for a psychedelic drug approval.<sup>10</sup>

#### CONCLUSION

Development of a psychedelic drug for treatment of a serious psychiatric disorder presents significant, although not insurmountable, challenges. While development will likely be perceived as high risk by the FDA and the DEA, precedent does exist for the development and approval of high-risk, CSA Schedule I drugs for serious conditions with unmet need. Treatment-refractory PTSD or similar targets in 2017 may be viewed as AIDS-related anorexia, as was in the development of Marinol in the 1980s.

Defining the clinical indication, likely an unmet medical need, addressing market and commercial issues, finding treatment settings to safely test and use such drugs, and mitigating postmarket risks are all requisite components. Special FDA approval pathways may facilitate an IND and, ultimately, an NDA for a carefully defined indication and patient population (e.g., Major Depression with suicidal ideation refractory to approved therapies).

Additional potential benefits of ongoing basic and clinical research with such agents may be further elucidation of the neurobiology—and phenotypic relationships—for specific mental and behavioral disorders.

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#### DISCLOSURES

Dr. Sellers is Professor Emeritus at the University of Toronto. In addition, he is a Principal in DL Global Partners Inc. DL Global provides independent consultation on a fee

for service basis to the pharmaceutical and device industry concerning psychotropic drug development and assessment of abuse potential. He has no conflict of interest concerning development of psychedelic drugs. Dr. Leiderman, former Director, Controlled Substance Staff, CDER/FDA, and Clinical Trials program director at NIDA/NIH, provides consultation in drug development and regulation through an independent consultancy. A Board Certified Neurologist and Fellow, American Academy of Neurology, she has served as a Consultant Neurologist within the VA Medical System and the US Public Health Service/Indian Health Service. She has held academic appointments in the Departments of Neurology at the University of Michigan and Uniformed Services University of the Health Sciences. She has no conflict of interest concerning development of psychedelic drugs.

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