COMMENTARY

Psilocybin: Good Trip or Bad Trip

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Much of the history of pharmacology and therapeutics involves finding new uses for old drugs. The latest rediscovery is that of psychedelic drugs.[1] Since they can cause profound distortions of perception and were once used as part of religious ceremonies, such research may seem unusual at this time.

Two randomized blinded controlled clinical trials (the Johns Hopkins University trial (JHU) and New York University trial (NYU)) have reported impressive long-term reductions in anxious depressed mood, existential distress, and improved quality of life after single oral doses of psilocybin in terminal cancer patients.[2,3] Responses to these findings have ranged from cautious to enthusiastic, e.g., "alternative to first-line anti-depressants" and a "successful return of psychedelics to psychiatry."[4]

This commentary alerts this journal's readers to the results and highlights issues that temper short-term enthusiasm with future hope for treating mental disorders.

Psilocybin is in many species of *Psilocybe* mushrooms used for millennia in ceremonial contexts.[5] Most past hallucinogen research has been descriptive and uncontrolled; however, better exploratory studies in obsessive-compulsive disorder, major depression, various substance use disorders, and cluster headache have occurred in the past 20 years. Research has been limited because psilocybin is in Schedule I of the UN Psychotropic Convention (1971), which prohibits possession and use.

MECHANISM OF ACTION

Psilocybin undergoes hepatic first-pass biotransformation with conversion to psilocin, its active metabolite. Psilocin's mechanism of action is not fully known but current knowledge suggests new approaches to treat mental disorders.

Psilocin is a 5HT2A receptor agonist with some activity at 5HT2C and several transporters (e.g., serotonin and norepinephrine).[6,7] 5HT2A activation occurs in several brain network hubs where cells become more sensitive through depolarization.[1] A small subset of cells recruit other cells that enhance neuronal "avalanches" that destabilize local networks and change connectivity. The claustrum area is a key gatekeeper region with extensive connectivity throughout the brain, normally maintaining balance in the resting state or default mode network. Psychedelics may disrupt normal cortical integration and create a temporary unstable network that "resets" to a "healthy" state after the drug has been eliminated. Imaging studies demonstrate acute and postdrug changes in connectivity and default mode network activity.[1]

Understanding of acute and chronic neuropharmacologic mechanisms are evolving rapidly. The importance of drug induced antiinflammatory and immune responses, complex indirect allosteric and homostatic regulation of G-protein regulated proteins (e.g., 5HT2A receptors), transient and sustained effects on the genome and epigenome all point to a different framework for psychotropic drug development.[1,8]

PSILOCYBIN MECHANISM OF ACTION IN THE CONTEXT OF THE JHU AND NYU TRIALS

Evidence of efficacy of antidepressants and other medications in life-threatening diseases is limited.[9] In part, the mental response to imminent death is qualitatively different than other mental disorders and in some cases, time is too short for effective pharmacotherapy. In the context of progressive life-ending or threatening disease, psychotherapy seems helpful. Group supportive psychotherapy and other forms of psychotherapy can help patients feel more in control, reduce depressive symptoms and hopelessness, and improve social functioning and quality of life with longer survival.[9]

Psilocybin's mechanism of action could be entirely pharmacologic. However, in the JHU and NYU patients much more is going on. These authors postulate that the "mystical" psilocybin experience is the mediating event. However, both trials provided extensive, concurrent psychotherapy and supportive care by highly trained experienced staff (**Table 1**). The JHU trial was tailored to the psilocybin intervention including discussion of meaningful aspects of the participant's life, preparation for the psilocybin sessions, encouraging participants to "trust, let go and be open," and focus on novel thoughts and feelings that arose during sessions.[2] The NYU trial used more traditional medication-assisted psychotherapy based on existential and psychoanalytic interpersonal therapy.[3]

"Mystical" may be useful shorthand for a complex event, but from a psychotherapeutic perspective, future research needs to

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Table 1 Summary psilocybin trial features

Characteristic	Johns Hopkins University (JHU)	New York University (NYU)	Implication
Screened (*N*)	566	108	Highly selected patient population limiting generalizability of results. Such slow recruitment suggests few interested patients or a very small target population
Accepted/enrolled (*N*)	56	31	
Completed (*N*)	51	23	
Trial duration	October 2007 to November 2014	February 2009 to October 2014	
Accepted patients characteristics			Mostly Caucasian, highly educated living in major urban centers with access to tertiary medical care; many with past/current use of hallucinogens and cannabis in stable relationship and living arrangements. Probably a motivated patient pool with high expectancy of positive experience from trial
Sex (female %)	49	62	
Age (years ± SEM)	56.3 (1.4)	56 (SD 1.3)	
Race (Caucasian)	94	90	
Postgraduate education (%)	53	48	
Married or partner (%)	69	69	
Lifetime use hallucinogens (%)	45	55	
Recent cannabis/dronabinol use (%)	47	N/A	
Uses per month (mean ± SEM)	5.8 (1.3)	N/A	
Psychiatric symptoms/ diagnosis			Presence of adjustment disorders in life threatening cancer is not unexpected but few psychiatric pharmacotherapies have been directed primarily at this condition. Psychotherapy a more typical approach. Applicability of these results to other psychiatric conditions is not clear
Chronic adjustment disorder + anxiety	20	62	
Chronic adjustment disorder + anxiety and depressed mood	20	28	
Dysthymia	9	—	
Generalized anxiety disorder (GAD)	9	10	
Major depression (MDD)	25	—	
GAD + MDD	7	—	
GAD + dysthymia	2	—	
Medication for anxiety or depression after diagnosis but discontinued (%)	51	59	Consistent with expected past history and supports patients not satisfied with medications and willing to try something else
Design	Two session randomized blinded crossover separated by 5 weeks; enrollment; drug session #1 week 9; drug session 2 week 14; follow-up week 19; follow up week 40	Two session randomized blinded cross-over separated by 7 weeks; enrollment; drug session #1 week 3; drug session #2 week 10; follow-up week 19; follow-up week 40	First, structured prospective robust design with psilocybin or any psychedelic drug
Supportive care and psychotherapy contact	Focused supportive care Pre-drug meetings mean 3 sessions; mean total time = 7.9 h Meeting day after drug day #1 and drug day #2 each time = 1.2 h Meetings between drug session #1 and #2	Psychotherapy Pre-drug #1 3 sessions 6 h Post-drug #1 3 sessions 6 h Post-drug #2 3 sessions 6 h	At both sites each supportive session or psychotherapy involved two staff. Safety supervision and staff training and supervision very intense. Required large commitment by investigators and staff and patients

Table 1 Continued on next page

Table 1 Continued

Characteristic	Johns Hopkins University (JHU)	New York University (NYU)	Implication
	mean 2.7 times mean total time 7.9 h Meetings after drug sessions and study end Mean 2.5 times; mean total time 2.4 h 16.1	Post-drug On-going support and integration with therapist	
Study visits for primary data collection	Baseline Each drug administration day 5 weeks after each drug session (mean 37 days) Study follow-up Mean 211 days after drug session #2	Baseline Drug dose #1 day -1 Drug dose #1 Study day Study day +1 Study day +14 Study day + 42 Drug dose #2 day -1 Drug dose #2 Study day Study day +1 Study day +14 Study day + 42 Study end follow-up +26 weeks post-drug #2	
Study setting	Living room setting; two monitors; subject lay on a couch, eye mask; headphones with music. Constant staff presence	Couch made into a bed; emesis basin; room furnished with flowers and fruit; pictures of family, friends, pets; listen to music. Constant staff presence	Great attention to set and setting to ensure they supported the psychedelic experience. Would be hard to reproduce the setting except in specialized facilities
What were subjects told	Focus on inner experience as per previous study instructions; attain maximal therapeutic benefit	Participants encouraged to discuss the subjective experience to consolidate the memory of the experience	This likely reinforced prior experience of patients and their expectancies a contributed a major psychotherapy by psilocybin interaction factor to the responses

determine what amount, type, and component of support work best and in which patients. Obviously, well-trained and supervised staff and standardized approaches will be needed wherever psilocybin is part of treatment.

SCIENTIFIC ROBUSTNESS AND CAUSALITY

The JHU and NYU studies have many strengths, including multiple subjective endpoints and assessments by the patient, family, community observers, and clinicians. Notwithstanding the novelty and interesting results, aspects of the designs and conduct are problematic. **Table 1** indexes notable features of the trials. Of particular note are: the relatively small number of participants; highly selected populations (e.g., urban, Caucasian, high levels of education, prior use of hallucinogens and cannabis); highly structured study settings; intensive monitoring supportive care and psychotherapy; and a protracted trial duration. Neither trial adhered to international regulatory and pharmaceutical clinical trial standards, including independent audit and monitoring and data entry and verification. Both trials made adjustments to design during the study (e.g., dose reduction, changes in inclusion criteria).

Both trials made an attempt to be double-blind. In one case the "placebo" was a low dose of psilocybin and in the other niacin. Blinding of trials where a drug has obvious effects is difficult. While both studies used methodology far superior to older trials, within-subject crossover designs confound study population bias, patient expectancy, the impact of study set and setting, the interaction of the drug's effects with supportive care, and counseling. In both trials, blinded therapists and monitors were able to identify active drug session treatment. Patients were not asked.

FUTURE DEVELOPMENT

Dose selection

Both clinical trials used safe doses of psilocybin. The JHU trial adjusted doses downward because of clinical toxicity (nausea after the high dose) and in the low-dose group because of concern the dose was not sufficiently "placebo-like." Unanswered are what are the minimal effective doses and optimal doses and dosing regimen for any therapeutic indications? Phase II programs typically include a range of doses to answer these questions.

Publicly available blogs describe and advocate for use of microdosing of LSD

Table 2 Pharmacokinetics of psilocybin's active metabolite psilocin

	Oral Mean (SD) [range]	Intravenous Mean (SD) [range]
Number subjects (M/F)	6 (5/1)	6 (6/0)
C_{max} (ng/ml)	8.2 (2.8) [4.8–12.3]	12.9 (5.6) [7.1–23.1]
T_{max} (min)	106 (37) [85–180]	1.9 (1.0) [0.7–3.7]
$AUC_{0\text{-infinity}}$ (ng.ml/ml)	1,963 (659) [1,184–2,988]	240 (55) [168–329]
T1/2 (min)	163 (63) [106–272]	74 (20) [60–91]
Bioavailability (%)	52 (20) [30–69]	—

and psilocybin (e.g., http://thehustle.co/how-to-lsd-microdose). The use of repeated doses of "sub-therapeutic" doses of psychedelics or repeated larger dosing raises chronic safety concerns and challenges drug developers to think of novel dosing paradigms that circumvent acute toxicity.

Expand pharmacokinetics and pharmacogenomics

Limited pharmacokinetic data exist for psilocybin and its active metabolite (**Table 2**).[6,10] Larger studies of genetically diverse populations are needed to ensure dose exposure linearity. Whether drug concentrations can usefully anticipate clinical response is unknown. As for all psychoactive drugs, pharmacodynamic variation is probably large. Genetic variants of the 5HT2A and 2C receptors and other drug targets are known, hence some very sensitive and insensitive individuals probably exist. All future psilocybin clinical research should include pharmacokinetics and genotyping.

Need to meet modern safety standards

Despite much experience with psilocybin, regulatory and scientific standards have changed over the past 60 years. These standards will need to be met. Psilocybin's reproductive, molecular biologic, and genetic toxicology is very limited. Most data relate to single doses and not multiple dose exposures. In particular, long-term behavioral safety in populations with risk factors and mental disorders will need study with prospective designs.

High abuse potential

Psilocybin can produce profound alterations in perception including illusions, synesthesia, affective activation, altered thought, and time sense. These are the reasons psilocybin is judged to have high abuse potential from a drug safety perspective. Whether it produces dependence is not critical. A safety problem arises with use in uncontrolled settings, with unknown doses involving possible diversion and no quality control of purity. If ever approved, psilocybin will be scheduled as C-II under the Controlled Substances Act.

An approvable indication

Psilocybin has been proposed to treat a number of disorders and medical conditions. However, no adequate controlled trials for any of these have been conducted and no bridge built to practical use. The JHU and NYU trial's extensive efforts to select patients, prepare them for the experience, train staff, develop a safe environment for drug administration, supervise patients, and select doses and monitor drug effects and safety are unrealistic for general use.[11] A mandated Risk Evaluation and Mitigation Strategy (REMS) with restricted conditions of use will be needed.

Another practical issue is that no precedent exists for approval of a drug for adjustment disorder-related anxiety and/or depression in life-threatening situations requiring structured psychotherapeutic support. Some paths to limited approvals such as orphan drug designation, among others, might be possible. This might facilitate speed of development, provide some marketing protection, and match the intervention to an unmet medical need in highly selected patient populations.

Drug development and commercialization pathway

A challenge for any repurposed off-patent drug is that few companies or investors will want to develop such a drug without strong intellectual property protection. To date, psilocybin research has been largely supported by individuals, private Institutes and Foundations (e.g., Heffter Research Institute, Riverstyx Foundation) committed to the area. Such advocacy is often essential to developing new opportunities. However, the costs and expertise needed for preclinical and clinical development, regulatory compliance, and interactions with the US Food and Drug Administration (FDA) are usually seriously underestimated. Further work using patentable novel, substituted tryptamines may be worth exploring.

CONCLUSION

In carefully controlled settings, psilocybin can be administered safely from a cardiovascular and neurologic perspective. Psilocybin appears to reduce anxiety and depression in life-threatening cancer. Further scientifically robust trials in this population and other therapeutic areas will help to establish the efficacy, safety, and pharmacokinetics and refine settings where treatment can occur. If old or new drugs can "reset" neural networks, many patients with serious chronic mental disorders could benefit. Models for mechanism of psychopharmacologic intervention are changing rapidly. The announced death of drug development in psychiatry by the pharmaceutical industry may be premature.

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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. None of this work has involved psilocybin or related substances.

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