Psychiatry's Risky Gamble on Recreational Drugs: The Royal Road to the Unconscious or Down a Pharmacologic Garden Path

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Commentary *Article*

Psychedelics: we first must enlarge our knowledge of how these work, what clinical conditions should be targeted, and how different psychedelics compare to each other.

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COMMENTARY

"Sometimes it's better to be lucky than smart."

-Louis "Lefty" Gomez, New York Yankees Pitcher

Just when the field of psychiatry had established its scientific bona fides and returned to the mainstream of medicine, this historically challenged medical specialty finds itself in the throes of a high-stakes socio-scientific experiment which, if successful, could provide therapies for conditions currently lacking effective treatment, and perhaps also offer extraordinary salutary benefits to the humanity. In raising such profound expectations, however, its failure could cause serious damage to the credibility of psychiatric medicine.

This would not be the first time that psychiatry courted reputational disaster. In the 1960s, psychiatry came perilously close to extinction when a reform movement—a century in the making—coalesced in response to diverse developments, including disenchantment with Freud's psychoanalytic theory which dominated the first half of the 20th century, public

outrage at the squalor in state mental hospitals revealed by media exposes, and scholarly assaults on the conceptual framework and nosologic validity of mental illness by intellectuals. This ultimately included the alliance between Thomas Szasz (author of *The Myth of Mental Illness*) and L. Ron Hubbard (founder of Scientology) to form the foundation of what evolved into the anti-psychiatry movement.

This near-death experience was averted by the reconceptualization of psychiatric nosology and commitment to the scientific method. But the danger is different this time.

In less than 2 decades, many previously illegal psychoactive substances have gone from recreational intoxicants to prescription pharmaceutical candidates based on claims of near miraculous therapeutic properties, a situation that causes me both excitement and worry. My excitement is narrowly focused on the opportunity to continue research on the classical psychedelics (lysergic acid diethylamide [LSD], mescaline, psilocybin, dimethyltryptamine) and their synthetic chemical analogues, which was abruptly interrupted decades ago, and clinically apply the resultant therapeutic benefits that may have enormous-but-as-yet-unproven benefits. If confirmed, this would constitute a monumental advance in psychotherapeutics: adding to current treatments for mental disorders, but also potentially causing an inflection point in the evolution of humankind by the expansion of human awareness and consciousness.

Consider Aldous Huxley's rapturous description of mescaline in *The Doors of Perception* as "the most extraordinary and significant experience available to human beings this side of the Beatific Vision."[1] No wonder naturally occurring psychedelics have been used ritualistically for centuries by Indigenous peoples. However, they did not come to the attention of medical science or the pharmaceutical industry until Albert Hoffman, a chemist at the Swiss drug company Sandoz (now Novartis), synthesized LSD. Clinical psychiatrists were so exhilarated by the enormous supposed potential of these substances that, by the mid-1960s, over 50,000 US patients had been treated with Delysid (the trade name for LSD) and over 1000 scientific papers and books were published.[2-7]

Meanwhile, countercultural icons Timothy Leary and Ken Kesey exhorted the public to "turn on, tune in, and drop out," propelling recreational psychedelic use far ahead of scientific research and clinical development.[7] Undesirable notoriety also came from increasingly disturbing associations, such as the Manson Family and the CIA ULTRA interrogation program, and the increasing incidence of emergency department visits for "bad trips."

By 1973, the government's perception of the dangers of psychedelics to American society had overshadowed their therapeutic promise. They were abruptly reclassified as Schedule I drugs "with a 'high potential for abuse and no currently accepted medical use,'" effectively banning research and clinical use of pharmacologic agents that might open new pathways to explore the human mind and consciousness, as well as novel treatments for behavioral disorders, for 4 decades.[8]

Despite the staunch efforts of a few scientific stalwarts (eg, Franz Vollenweider, Rick Strassman, David Nichols, David Nutt, and Bryan Roth) and self-styled therapists and healers using improvised methods, the knowledge base of psychedelics remained frozen from 1973 through the first decade of the 21st century when socio-political conditions became conducive to renewed interest in psychedelic drugs as therapeutic agents and the freeze began to thaw.

Wherein lies the concern. While the potential value of psychedelics was appreciated, their uniqueness was not and were lumped in with other less potentially impactful recreational drugs (cannabis, ketamine, ecstasy, ibogaine, etc). This gives us a second chance to discover the true value of psychedelics, but as part of an anomalous situation unparalleled in modern medical history in which previously illegal psychoactive substances used predominantly for recreational purposes are being rolled out *en masse* as candidates for US Food and Drug Administation (FDA) approval as prescription pharmaceuticals. Even more shocking is the fact that some are also simultaneously being proposed for legalization and ready access.[9]

Following the path successfully forged by cannabis, psychedelics (psilocybin, mescaline, LSD, DMT), dissociatives (eg, ketamine, ibogaine) and empathogens (MDMA) are wending their way through the FDA approval process.

Compounding the situation, state governments—realizing that legitimization of outlawed drugs meant the creation of new industries, commercialization, and new sources of tax revenues—did a legislative about face incentivized and justified by acceding to the tsunami of the popular demand for legalization.

Consider cannabis, which went from a feared and forbidden substance (demonized in the 1936 documentary "Reefer Madness") to a $61 billion commercial gold-rush industry. It is now approved for medical use in 38 states (despite the fact that it has been FDA approved for only 1 clinical indication, the rare childhood seizure disorder Lennox Gastaut Syndrome), legalized for recreational use in 24 states, and decriminalized in an additional 7.

Ketamine is another example of the rapid rise and promiscuous use of a recreational drug. Developed as a milder version of phencyclidine (PCP or Angel Dust) by Parke Davis Co, it was originally a dissociative anesthetic used mainly for children and burn victims, (and popular as the club drug "Special K"). More recently it was found to be a highly effective, rapid-acting treatment for severe depression and suicidality. Almost immediately, ketamine clinics proliferated, offering this new wonder-drug for all manner of symptoms via different modes of administration and at various doses, all without sufficient supporting data. Such off-label reckless use has had tragic consequences, exemplified by Matthew Perry's death from ketamine-induced cardiac over-stimulation and respiratory depression.[10,11]

Which brings us to 2024. The FDA has already declined to approve MDMA-assisted psychotherapy as a treatment for posttraumatic stress disorder based on the New Drug Application submitted by its sponsor Lykos. Next in line for review will likely be Compass the sponsor of psilocybin for treatment-resistant depression in 2025, followed by Cybin and Mind Med.[12] While such developments should be welcome, I worry about a potential lack of scientific rigor in their development reflected by the opportunistic choice of their clinical indications worries me. The way things are headed, we will only find out if my concerns are warranted from the post-marketing experience following FDA approval.

That said, these cautionary comments should not be mistaken for a lack of enthusiasm about the potential salutary value of psychedelics. Rather, I believe that we first must enlarge our knowledge of how these work, in what clinical conditions they have proven efficacy, and how different psychedelics compare with each other. We must appreciate the profound importance of this opportunity and not fail to take full advantage of it. Toward this end, I have written 3 articles for publication in *Psychiatric Times*, this being the first, on the resurrection of previously recreational intoxicants for therapeutic purposes, and specifically the development and optimization of psychedelics for use in psychiatric medicine and by society. The second article will highlight key questions that must be answered about psychedelics and chemical analogues for us to truly and fully understand how these substances work and what they actually do. The third will discuss the socioeconomic, medical, and legal ramifications of liberalized access to psychedelics and how their medical and lay use will affect our society.

As psychiatry faces yet another watershed moment, it is my hope that these articles will increase awareness and focus attention on the importance and optimal pursuit of this unprecedented experiment in pharmaceutical development in which scientific dispassion and rigor have been hijacked by

unbridled enthusiasm and commercial opportunism. There is too much at stake for psychiatry and society.

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