

Maddening therapies: How hallucinogens morphed into novel treatments

In medicine we must always expect the unexpected. Medicine is replete with paradoxes, where poisons become cures.

Snake venom is deadly but is being used to treat some cancers,¹ because it produces contortrostatin, a protein that “paralyzes” cancer cells and prevents them from migrating. Venoms from spiders are being investigated as a treatment to slow the progression of muscular dystrophy by preventing muscle cells from deteriorating. Venom from tarantulas can relieve chronic pain, and those from centipedes help rodents tolerate thermal, chemical, or acid pain. Scorpion venom can cause cancer cells to glow under a flashlight, enabling surgeons to locate and remove them. Anemones toxin could be used to treat autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, and lupus.

Vaccines are an excellent example of how deadly pathogens can be transformed into life-saving therapies. Billions of people have been protected from polio, smallpox, tetanus, diphtheria, measles, mumps, rubella, influenza, pneumococcus, hepatitis A and B, rabies, shingles, typhoid, meningitis, or cholera. Turning killers into saviors is one of the most remarkable miracles of medical research.²

The mind-boggling transformation of mind-altering drugs

In psychiatry, psychedelic drugs have been repurposed into useful therapies for mental illness. As recently as a decade ago, psychiatric practitioners—physicians and nurse practitioners—regarded hallucinogens as dangerous, “must-avoid” drugs of abuse that could trigger or exacerbate serious psychiatric disorders. Then, thanks to ongoing research, the psychedelic “caterpillars” transformed into therapeutic “butterflies,” and the despised drugs of abuse became welcome adjuncts for treating some stubborn psychopathologies. Such paradoxical developments are emblematic of how one can always find a silver lining.

Consider the following transformations of various psychedelics and hallucinogens—also called “entheogens”—into novel pharmacotherapies. Note that in most cases, the application of these mind-altering drugs into useful medications is still a work in progress.

LSD

Lysergic acid diethylamide (LSD) was used extensively for treating mood disorders in the pre-antidepressant era, before it was prohibited in the late 1960s. A review of 19 studies—many uncontrolled—concluded that approximately



Henry A. Nasrallah, MD
Editor-in-Chief

Mind-altering drugs, once considered dangerous, are being investigated for treating depression, PTSD, anxiety, and other psychiatric illnesses

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Published through an
educational partnership
with Saint Louis University



80% of patients improved, according to the treating physicians.³ However, research on LSD was halted for several decades after it became illegal, and resumed in 2010. Neuropsychiatrists and neuroscience researchers are now employing advanced techniques, such as neuroimaging, molecular pharmacology, and connectomics, to study its therapeutic effects.⁴ LSD is not only being used for treatment-resistant depression but also anxiety, alcoholism, autism, and even schizophrenia. However, despite its potential uses for treating alcoholism and anxiety, enhancing creativity, or caring for terminally ill patients, using LSD requires expertise, caution, and adherence to ethical standards.⁵

In healthy individuals, the effects of LSD include visual hallucinations, audiovisual synesthesia, depersonalization and derealization, and a sense of well-being, happiness, closeness to others, and trust.

Biologic effects include increased heart rate and blood pressure, elevated temperature, dilated pupils, and increased serum cortisol, prolactin, oxytocin, and epinephrine. All effects subside within 3 days.⁶

Psilocybin

Psilocybin, a component of some mushrooms that is known for its use during rituals in some cultures, has been discovered to have antidepressant, anxiolytic, and anti-addictive effects.⁷ Recent controlled studies at Johns Hopkins University reported that a single dose of psilocybin can relieve anxiety or depression for up to 6 months, which, if replicated, could lead to a remarkable paradigm shift in treating mood and anxiety disorders, especially if patients do not respond to standard antidepressants.³ Other emerging uses of both psilocybin and LSD are in treating addictions⁸ where psychiatry is desperately looking for innovative new therapies.

Ecstasy

MDMA (3,4-methylenedioxymethamphetamine), also known as ecstasy, is widely regarded as a harmful party drug that produces euphoria, but not hallucinations. However, it has emerged as a useful treatment for post-traumatic stress disorder (PTSD). In one study of female sexual abuse victims, 80% of the patients who received MDMA with psychotherapy no longer met diagnostic criteria for PTSD after 2 months.⁹ Other studies showed no effects. Despite persistent skepticisms by many, the Multidisciplinary Association for Psychedelics Studies organization is investing millions of dollars into studying MDMA for PTSD in several countries.^{9,10} One hurdle is that it is difficult to conduct truly blind studies with psychedelic drugs because of their profound effects. MDMA releases cortisol, oxytocin—which are known to facilitate psychotherapy—and testosterone, but the debate about the risk-benefit ratio will continue.¹¹ MDMA also is being studied for treating social anxiety in adults with autism.¹²

Ketamine

Ketamine is a weaker cousin of the potent psychotogenic phencyclidine (approximately one-fiftieth the potency) and is a well-known drug of abuse that causes dissociation and hallucinations. It is used as an anesthetic in veterinary medicine and in children undergoing surgical procedures. Until recently, its only use in psychiatry has been as an anesthetic during electroconvulsive therapy. However, over the past few years, IV ketamine has been in the spotlight as a breakthrough, rapid-onset antidepressant and anti-suicidal agent in several controlled studies.¹³ This drug is revolutionizing the management of treatment-resistant depression and suicidal ideation and generating new insights into the neurobiology of depression.

Cannabis

Last, but certainly not least, is marijuana, which is more widely used than all the other psychedelics combined, and is currently at the center of a national debate about its legalization. Although the director of the National Institute on Drug Abuse highlighted the many risk of marijuana,¹⁴ studies have pointed to the myriad medical uses of *Cannabis*.^{15,16} An editorial in *Nature Medicine* recently urged that regulators reconsider the tight constraints on marijuana research.¹⁷ Some of the medical applications of marijuana include:

- **psychiatry** (anxiety, PTSD)
- **neurology** (severe epilepsy, tremors in Parkinson's disease, traumatic brain injury, pain of multiple sclerosis, muscle spasms, and progression of Alzheimer's disease)
- **oncology** (nausea and pain of chemotherapy, reduction of metastasis)
- **ophthalmology** (decrease of intraocular pressure in glaucoma)
- **autoimmune disorders** (rheumatoid arthritis, Crohn's disease, lupus).

However, as a schizophrenia researcher, I am wary about marijuana's high risk of triggering psychosis in young adults with a family history of schizophrenia spectrum disorders.¹⁸

The above are examples of how psychiatry is finally recognizing the therapeutic value inherent in traditionally "evil" street drugs that we euphemistically refer to as "recreational drugs." Even methamphetamine, the universally condemned and clearly harmful drug, was recently reported to be neuroprotective at low dosages!¹⁹ Could our field have suffered from a blind eye to the benefits of these hallucinogens and ignored the possibility that some persons with addiction who use these "recreational drugs" may have been self-medicating to alleviate their undiagnosed psychiatric disorder? We need to reconceptualize the pejorative term "mind-altering drug" because of

its implicitly negative connotation. After all, alteration may indicate a favorable, not just a deleterious, outcome.



Henry A. Nasrallah, MD
Editor-in-Chief

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We need to reconceptualize the term 'mind-altering drug' because of its implicitly negative connotation; alteration may indicate a favorable, not just a deleterious, outcome