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Psychedelic drugs exist at the intersection of sociological and pharmacological inquiry, occupying a niche that few other substances do. What we sense, feel, and perceive informs our interaction with the world around us, and ultimately, our human experience. The transformation of this experience by psychedelic drugs has had profound effects on culture, society, law, science, and medicine. Fundamentally, psychedelics are just a chemical that interacts with our nervous system, but the implications of their effects has complicated almost every sphere they exist within. Through the lens of psychedelics, we can explore the answers to questions in science, sociology, and medicine: the dichotomy of the natural and the synthetic, the interplay between recreational and spiritual purpose, and the therapeutic implications of untraditional substances. However, the psychoactive experience is just as much a complicated intersection of ideas, beliefs, and history as it is a powerful investigative tool.

All psychedelics, and several non-psychedelic drugs, like opioids, are considered psychoactive–they are substances that affect how the brain works and cause changes in mood, awareness, thoughts, feelings, or behavior (National Institutes of Health). Hallucinogens, however, cause more intense changes in the subjective experience than other psychoactive drugs. “Hallucinogenic” is occasionally used interchangeably with “psychedelic,” although here, psychedelics are considered a subcategory of hallucinogens rather than a synonym (Nichols). Also known as “classical hallucinogens”, these psychedelics include some of the more well-known hallucinogenic drugs: psilocybin, a naturally occurring substance found in mushrooms; lysergic acid diethylamide (LSD), which is made from a substance found in the ergot fungus; dimethyltryptamine (DMT), which is found in some trees native to Central and South America, and mescaline, which is derived from the Mexican peyote and San Pedro cacti (Nichols). The broader category of hallucinogenic drugs includes dissociatives and deliriants in addition to psychedelics, although they are usually not the focus of scientific and medical research on hallucinogens (National Institute on Drug Abuse). Dissociatives and deliriants do hold wide therapeutic potential, however. Antiglutamatergic dissociative drugs, like nitrous oxide and ketamine, have established medical use in anesthesiology and depression treatment, respectively (Krupitsky and Grinenko). Likewise, GABAergic deliriant drugs, like Ambien, are used as sedatives and insomnia treatments (Salvà and Costa).

Psychedelics are categorized together on the basis of their serotonergic mechanism of action. They serve as agonists of the 5-hydroxytryptamine 2A (5-HT2A) receptor, a major excitatory G protein-coupled receptor for serotonin (Nichols). In particular, they bind to 5-HT2A receptors that are expressed in neocortical pyramidal cells–important computation units in the brain that receive input from almost all subcortical and unconscious processes (Eyal et al.). According to prominent medicinal chemist David E. Nichols, research with serotonergic psychedelic compounds may help elucidate “roles that these receptor systems may play in normal cognitive function” (Purdue University). Psychedelic research also helps further

characterize the 5-HT2A receptor and its binding mechanism, information which could allow scientists to develop vast amounts of novel therapeutic drugs that bind to the receptor (Kim et al.).

Although the scientific progress informed by psychedelic drug research has pushed the boundaries of the field of psychopharmacology, these compounds are surrounded in legal red tape by virtue of their psychoactive nature. The 1940s, 50s, and 60s were characterized by a boom in popular and scientific interest in psychedelics, and extensive research and testing was conducted on LSD and other hallucinogenic compounds (Petranker et al.). However, as popularity of their recreational use soared, a combination of misinformation, misuse, and rising conservatism led to their international prohibition in 1971. Scientific research on psychedelics was effectively halted until the 21st century, when interest in psychedelic research was rekindled by the efforts of the Multidisciplinary Association for Psychedelic Science (MAPS), as well as a growing mental health epidemic and entrepreneurial interest in a lucrative new market (Petranker et al.). Despite a surge in research, psychedelics are still classified as Schedule I in the United States, which is reserved for drugs with “high abuse potential; no accepted medical use; and lack of safety even under medical supervision” (United States Drug Enforcement Administration).

The persevering illegality of recreational psychedelic use has inadvertently resulted in “designer drugs", formally known as New Psychoactive Substances (NPS), coming to prominence in both society and media. The clandestinely synthesized NPS are manufactured in such a way that they mimic the pharmacological effects of controlled substances, while skirting legality due to slightly different chemical structures (Schifano et al.). Although these drugs may operate through a loophole in the austere laws surrounding classical hallucinogens, their clandestine–and often chemically primitive–synthesis and the lack of robust testing means they can be particularly dangerous (Schifano et al.). Synthetic marijuana, also known as K2 or Spice, is a NPS that contains synthetic psychoactive chemicals that mimic the action of tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana. Unlike naturally occuring marijuana, synthetic marijuana has been linked to a number of fatal heart attacks in users, as well as seizures, uncontrollable body movements, and blackouts (Centers for Disease Control and Prevention). Recently, there have been reports of synthetic marijuana-induced psychosis, hallucinations, and violent behavior, with symptoms far more severe and longer-lasting than those observed from naturally-derived cannabis.

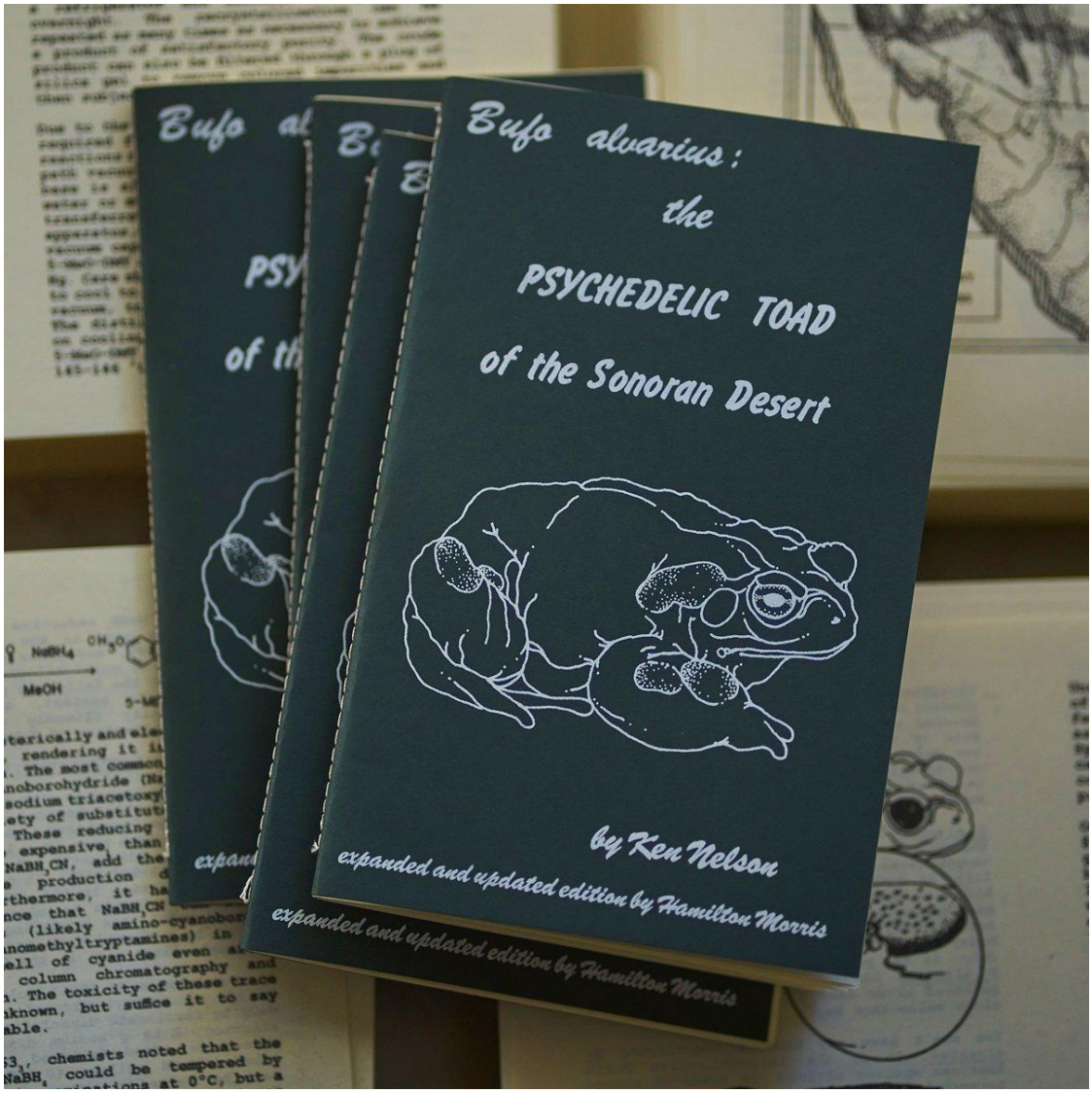
The rise of laboratory-synthesized psychedelics like NPS have introduced what some in the psychedelic community believe is an important dichotomy: naturally-derived vs. laboratory-synthesized psychedelics. The mere existence of this difference is debated–many spiritually-inclined psychedelic users believe that the phenomenon of natural occurrence lends an inherent significance to naturally-derived hallucinogens, while psychedelic scientists argue that the identical chemical structures of naturally-derived and laboratory-synthesized psychedelics makes them functionally equivalent (Samorini and Montgomery). 5-MeO-DMT, a close relative of DMT, provides an interesting case study of this issue. Although found in a variety of plant species, 5-MeO-DMT is endogenous to one unique animal: the Sonoran Desert toad, *Bufo alvarius* (Weil and Davis). Largely unknown by the burgeoning psychedelic community in the early 1980s, 5-MeO-DMT was catapulted into the spotlight by the 1983 publication of *Bufo alvarius: the Psychedelic Toad of the Sonoran Desert* by Ken Nelson, an

environmentalist and independent researcher from Denton, Texas (Siebert). Nelson, considered the first to have ever consumed *B. alvarius* venom, realized that the Sonoran Desert toad provided the first natural source of 5-MeO-DMT in North America. With the new attention commanded by the publication of Nelson's pamphlet, the Sonoran Desert toad began to develop a cult-like following, as pioneering "psychonauts" traveled en masse to gather and smoke the toad venom.

However, as is often the case when a plant or animal possesses a high-demand resource, the widespread popularity of 5-MeO-DMT has significantly threatened the existence of *B. alvarius*. The removal of the toad from its natural habitat, as well as harmful venom "milking" processes, has caused its population to significantly dwindle (Vedøy Uthaug). This is compounded by the development of highways through the Sonoran Desert, where the toads, hunting the insects that are attracted to the roadside lights, are often killed by vehicles. As a result, *B. alvarius* has been designated as 'endangered' in California, and 'threatened' in New Mexico (Lower Colorado River Multi-Species Conservation Program).

What makes the plight of the Sonoran Desert toad so tragic is that 5-MeO-DMT is not only easily artificially synthesized but has been for over 80 years. 5-MeO-DMT was first synthesized in 1936, and in the present day, can be made relatively easily and cheaply with readily available chemical precursors (Shen et al.). According to documentarian and psychedelic researcher Hamilton Morris, "One person can produce enough 5-MeO-DMT to supply everyone that would ever want it" (Siebert). Safety is not a justification–designer drugs are dangerous because of the slight structural differences from the original molecule, resulting in unforeseen adverse psychological and physiological reactions. Unlike synthetic marijuana and other NPS, synthetic 5-MeO-DMT is identical to *B. alvarius*-derived 5-MeO-DMT. Morris interviewed Nelson recently on his psychedelic documentary show, *Hamilton's Pharmacopeia*, as part of an episode exploring 5-MeO-DMT and *B. alvarius*. Nelson, who arguably discovered the psychedelic use of *B. alvarius*, expressed disappointment with its ecological repercussions, urging users to look to synthetic sources (Morris and Nelson).

Despite a simple synthetic alternative and pleas from the pioneer of 5-MeO-DMT, many users of *B. alvarius*-derived 5-MeO-DMT are hesitant to abandon their natural source. Users who find spirituality in the venom, and often the toad itself, believe that the "spirit" of the toad changes the experience (Samorini and Montgomery). Although there is no scientific basis for this belief, there is an undeniable psychological modulation of the experience accomplished by the phenomenological presence of a psychedelic compound in an animal. In a speech at the 2019 World Bufo Alvarius Congress, Morris explained, "I think that we often underestimate our own contribution to these experiences–we tend to assign it to the drug, but not to ourselves. There's something important, interesting, and valuable about something coming from a toad. It's very strange… to know that this came from a living organism, that it was a defensive material that they created as opposed to something that was made in a laboratory… it changes things without any kind of supernatural overlay." (Morris)



The expanded 2020 edition of *Bufo alvarius: the Psychedelic Toad of the Sonoran Desert*, Nelson's original 1983 publication that brought 5-MeO-DMT into the psychedelic mainstream. Image source: Hamilton Morris (2020), https://twitter.com/HamiltonMorris

As *B. alvarius* has shown, the distinction between naturally-derived and laboratory-synthesized psychedelics is often non-chemical. By assigning spirituality or cultural significance to a substance, the nature of the psychedelic experience transforms into something much more mystical, a trait sought after by the many psychedelic users who seek life-changing, emotion-altering experiences. Naturally-derived psychedelics, like the DMT found in the Ayahuasca plant, or the mescaline found in the Peyote cactus, have found popularity among nonindigenous Westerners as a means of undergoing something akin to a religious experience. Ayahuasca has a profound cultural impact among indigenous groups of the Amazon, where the plant has been used for religious and medicinal purposes as early as 900 B.C (Walubita). Peyote has been used by native North Americans for even longer, likely five-and-a-half thousand years (El-Seedi et al.). The religious ceremonies involving these drugs are led by a Shaman, who acts as the mediator of the proceedings and psychedelic experience. In addition

to traditional preparations to extract the compound from the plant, the Shaman follows specific rituals and procedures not necessary for consuming the drug, but which hold ceremonial importance within the varying cultures. This includes acts like drumming and chanting, which are intended to heighten the experience and create a feeling of connection with the spiritual world (Sessa).

A person from the *Comanche* indigenous tribe plays drums in a peyote ceremony (circa 1927). Image source: Edward Curtis (1927)

In indigenous communities, these ceremonies provide not only a means to increase social cohesion, but to engage with cultural practices and resist assimilation into the Western mono-culture (Sessa). After hundreds of years of discrimination, forced displacement, and persecution because of traditional use of plant-based hallucinogens, these ceremonies hold significant cultural importance and highlight the West's fascination with naturally-derived psychedelics. Although ceremonial practice is not necessary to have a psychedelic experience

per se, it is important to consider the cultural and spiritual context of indigenous practices when utilizing hallucinogens for therapeutic purposes. In an article published in the Journal of Psychedelic Studies, George et al. writes, “The scientific progress and clinical promise of this movement [psychedelic medicine] owes much of its success to the history of indigenous healing practices; yet the work of indigenous people, ethnic and racial minorities, women, and other disenfranchised groups is often not supported or highlighted in the mainstream narrative of psychedelic medicine.”

With an understanding of the indigenous cultural context and history of psychedelic medicine, the future of therapeutic usage looks promising. Ibogaine and peyote, psychedelics with significant indigenous history, are currently being studied as potential treatments of substance abuse (Brown and Alper; Fickenscher et al.). There is evidence psilocybin-assisted therapy can decrease symptoms of depression and anxiety and has potential to assist in the treatment of a multitude of other disorders like addiction, anorexia, and Alzheimer’s disease (Carhart-Harris et al.; Grob et al.; Lewis). Even LSD, which has not typically been associated with therapeutic use, is indicated as a safe and effective way to ease end-of-life anxiety, depression, and addiction (George et al.). Despite the nascent scientific research and a lack of recognition from the government, the therapeutic potential of psychedelic drugs is immensely and excitingly vast.

The influence of psychedelics on chemistry, neuroscience, law, ecology, sociology, medicine, and more is profound. However, when such an influential substance can powerfully transform the human experience, it will inevitably have a complicated existence. Through building an understanding of the myriad roles psychedelic drugs play, we can use them to improve science, society, and ultimately–ourselves.

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