



Ancient Roots of Today’s Emerging Renaissance in Psychedelic Medicine

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Abstract An international ban on psychedelics initiated by the United Nations’ Convention on Psychotropic Substances in 1971 restricted the clinical use of these ancient psychoactive substances. Yet, in an era marked by rising mental health concerns and a growing “Deaths of Despair” epidemic (i.e., excess mortality and morbidity from suicide, drug overdose, and alcoholism), the structured psychedelic use that has long been a part of ritual healing experiences for human societies is slowly regaining credibility in Western medicine for its potential to treat various mental health conditions. We use a historical lens to examine the use of psychedelic therapies over time, translate ancient lessons to contemporary clinical and research practice, and interrogate the practical and ethical questions researchers must grapple with before they can enter mainstream medicine. Given the COVID-19 pandemic and its contributions to the global mental health burden, we also reflect on how psychedelic therapy might serve as a tool for medicine in the aftermath of collective trauma. Ultimately, it is argued that a “psychedelic renaissance” anchored in the lessons of antiquity can potentially help shift healthcare systems—and perhaps the broader society—towards practices that are more humane, attentive to underlying causes of distress, and supportive of human flourishing.

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In 2008, archaeologists excavating a cave in the Sora River valley in southwestern Bolivia discovered a 1,000-year-old ritual bundle formerly belonging to a shaman of the pre-Inca Tiwanaku civilization. Scrapings from the artifacts inside revealed traces of psychotropic compounds—benzoylecgonine (a metabolite of cocaine), bufotenine (an alkaloid in psychedelic snuff powder), psilocin (the active agent in magic mushrooms), and harmine and dimethyltryptamine (the active ingredients in the psychedelic tea known as ayahuasca) (Miller et al. 2019).

Use of psychoactive substances in healing practices is often associated with “shamanism”, although the practice was so ubiquitous in the ancient world that it should effectively be considered a species “norm”. Ritual use of drugs has often been associated with hunter-gatherer cultures across the globe—from the Americas, to Eurasia, to Australia, and Africa (Walter and Fridman 2004). However, there is no reason to believe that hunter-gatherers are the only societies in which psychoactive substances have been of central importance. Writing in the fourth century BC, Herodotus described ritual use of cannabis by the Scythians of the Pontic Steppe, a practice recently corroborated by archaeological analysis of braziers used in funerary rites (Ren et al. 2019). The ancient Greeks—and later the ancient Romans and agrarian societies in the near east and Minoan Crete—held the Eleusinian Mysteries, seasonal religious rites that included ritual ingestion of a psychoactive drink called kykeon, which evidence has shown may have included ergot fungi containing LSD-like psychedelic alkaloids (Samorini 2019; Wasson, Hofmann, and Ruck 1978; Ouvaroff 1817). Moreover, the *soma* drink described in the Rigveda clearly refers to a non-alcoholic psychoactive substance, although its precise identity is a matter of debate (Staal 2001). A related libation, *hoama*, is also prominent in the Avestas, the ancient scriptures of Zoroastrianism. Ancient American societies also appear to have embraced psychoactive ritualism to an exceptional degree, including those that were urban and made use of writing, such as the Maya (Dobkin de Rios 1974).

Indeed, while the materials discovered in the Bolivian cave were exceptional for their preservation and diversity, there is nothing remarkable about the ancient use of psychedelics per se. What *is* unusual is the active *suppression* of such substances, a late twentieth century global phenomenon led by the United States and United Nations (albeit with deeper roots in Christianity and the colonial Americas) (Carod-Artal 2015). Today, some healers in Western countries still employ psychoactive plants, often illicitly due to the still-binding international bans on psychedelics initiated by the UN’s Convention on Psychotropic Substances of 1971 (Nutt et al. 2013).

But in our current era marked by growing mental health concerns (Vahratian et al. 2021), prohibitions against compounds that have long played an integral role in mediating mental and spiritual health in human societies feel increasingly out-of-step. Indeed, the early twenty-first century has not only ushered in rising depression

and anxiety (Lim et al. 2018; Ettman et al. 2020), but also a crisis of “Deaths of Despair” (DoD)—excess mortality and morbidity from suicide, drug overdose, and alcoholism, especially among working class adults in mid-life with low educational attainment (Case and Deaton 2020, 2021; Brignone et al. 2020; George et al. 2021). These self-harming deaths, which are strongly linked to growing feelings of distress (Blanchflower and Oswald 2020), loss of social cohesion (Case and Deaton 2020; 2017; 2015; Marmot 2018; Scutchfield and Keck, 2017; Stein et al. 2017), isolation and disconnection from social institutions (Smeraldo et al. 2020), and loss of hope for the future, are estimated at 150,000 per year in the US. DoD are rendered even more socially damaging by distal factors such as access to handguns and lethal drugs (e.g., fentanyl) (Shiels et al. 2020; Well Being Trust 2021), that, taken together, have contributed to an annual downward trend in life expectancy in the US from 2015 to 2017, representing the longest sustained decline since 1915–1918 (Murphy et al. 2018).

While DoD were initially characterized as a phenomenon disproportionately affecting non-Hispanic white populations in economically-distressed regions, including the Midwestern “Rust Belt” and Appalachia (Case and Deaton, 2015; Dwyer-Lindgren et al. 2017), more recent evidence suggests that the crisis of rising despair-related mortality extends across racial, ethnic, and gender groups as well as geographic locales and generational cohorts (i.e., Millennials) (Sheils et al. 2020; Well Being Trust 2020; Gaydosh et al. 2019; Woolf and Schoomaker 2019; Case and Deaton 2021). So too have upticks in despair-related mortality recently been observed in other Western countries, including the UK, Canada, and Australia (Case and Deaton 2020). It seems that despair is proliferating in an era defined by globalization, deindustrialization, deunionization, and increasing automation, as well as historic recessions, record income and wealth inequality, prolonged wage decline, austerity cuts to social safety nets (Case and Deaton 2020), and now a global pandemic that has exacerbated these systemic failures (Vahratian et al. 2021). As structural conditions have broadly worsened for the working class, development of novel pharmacologic approaches for mental health maladies have stagnated, attributable in part to growing interest in non-pharmacological treatments (Wortzel et al. 2020), a substantial shift in funding by the National Institutes of Mental Health—the world’s largest funder of mental health research—from clinical trials to basic research (Reardon 2017; Lewis-Fernandez et al. 2016) and calculated decisions by pharmaceutical companies to pursue treatment for conditions with lower risks and higher profit-margins (Miller 2010).

This confluence of historical conditions has, in part, set the stage for psychedelics to reemerge from the realm of taboo. Although these compounds remain criminalized, in recent decades one sanctioned space has continued to explore their use: clinical research. While the shaman of the Andes might look askance at the biomedical laboratories where scientists now study altered states, these clinics have become a major proving ground for the re-legitimation of psychedelics in Western culture (Garcia-Romeu et al. 2016; Reiff et al. 2020). (see Fig. 1).

In the last decade alone, governing bodies have approved clinical trials on MDMA, ketamine, LSD, psilocybin, and dimethyltryptamine—the latter two of which were also part of the Tiwanaku shaman’s ancient armamentarium (Siegel



Fig. 1 Top, a cave in the Sora River valley in southwestern Bolivia where researchers discovered a 1000-year-old ritual bundle formerly belonging to a shaman of the pre-Inca Tiwanaku civilization; below, the building currently housing the Johns Hopkins Center for Psychedelic and Consciousness Research

et al. 2021). There has, in turn, been a burgeoning of peer-reviewed research establishing preliminary effectiveness of these therapies in treating depression (Carhart-Harris et al. 2021; Davis et al. 2020), substance use disorders (Bogenschutz et al. 2015; Johnson et al. 2014), PTSD (Mitchell et al. 2021), and anxiety for

patients facing terminal cancer (Griffiths et al. 2016; Grob et al. 2011; Ross et al. 2016). New studies are beginning to examine psychedelics as potential treatments for other wide-ranging conditions such as eating disorders, migraine and cluster headaches, and early dementia (Siegel et al. 2021).

Research has concurrently sought to identify mechanisms underlying the effectiveness of such treatments. While classic psychedelics like psilocybin, LSD, and ayahuasca exert their primary effects via the serotonin 2A (5-HT_{2A}) receptor that is heavily expressed throughout the cortex, other hallucinogenic compounds such as ketamine act on glutamatergic N-Methyl-D-Aspartate receptors, with both inducing neuroplastic changes that may lead to therapeutic benefits (Deyama and Duman 2020; Ly et al. 2018). Additionally, the classic psychedelics have been found to initiate a cascade of altered neural connectivity and blood-flow across brain regions including the “default-mode network” (medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule, lateral temporal cortex, hippocampus, and precuneus), amygdala, thalamus, and claustrum, disrupting established patterns of brain activity and altering a person’s fundamental sense-of-self (Barrett et al. 2020; Kraehenmann et al. 2015; Preller et al. 2018; Roseman et al. 2018a,b).

Data indicate these changes correspond with the altered states that have for millennia precipitated mystical, meaningful, and transcendent experiences often characterized by profound feelings of connection, openness, and unity, and there is compelling evidence that the numinous quality of acute psychedelic experiences may itself be predictive of long-term clinical changes in mental health (Bogenschutz et al. 2015; Garcia-Romeu et al. 2014; Griffiths et al. 2016; Roseman et al. 2018a,b). Given that many mental health conditions are marked by inflexible patterns of habitual thought, feeling, and behavior (Morris and Mansell, 2018), using psychedelics to disrupt neural systems encoding such patterns provides a compelling approach for mental healthcare treatment (Carhart-Harris et al. 2014). Furthermore, the seeming ability of psychedelics to enhance cognitive, emotional, and creative flexibility, in part by evoking the mystical-type experiences long sought out by our human ancestors, can be a powerful starting point for psychological healing (Nutt and Carhart-Harris 2021; Davis et al. 2020; Mason et al. 2021; Harris, 2021). Coupled with therapeutic integration focused on insight and emotional recalibration, and in light of psychedelics’ ability to promote structural and functional neural plasticity, these substances may actually help “rewire the brain” to enable long-term relief.

Indeed, beyond psychoactive compounds themselves, non-pharmacological variables have been shown to significantly impact individuals’ experiences on psychedelics (Studerus et al., 2012). According to one review, “the effects of hallucinogens are heavily dependent on the expectations of the user...and the environment...in which the use takes place” (Nichols 2004, p. 137). At least with respect to psilocybin, the psychological and emotional state of the user in the 4-weeks prior to their psychedelic episode are extremely important in determining whether the subject experiences severe anxiety (i.e., a “bad trip”) or has a more positive, “spiritual” encounter with what twentieth century psychologist Carl Jung famously described as the “sphere of numinous experiences” (in Hill 2013; Studerus et al. 2012).

It is therefore notable that anthropological accounts of ayahuasca medicine in indigenous Amazonian communities often emphasize the importance of a knowledgeable and experienced *curandero* (healer) to act as a guide, as well as the need for days, or even weeks, of appropriate preparation in advance of actually drinking the psychedelic brew. Consider the following words of Guillermo Arrévalo, a Shipibo shaman who works in Pucallpa, Peru: “I have to organize my work around what the person accepts as their beliefs about what it is that has damaged them, the particular trauma involved. On this basis, *I organize the psychological part of the person*, which enables me to understand and to see the solution to their problem” (Dobkin de Rios 2005, p. 204; our emphasis). As reflected in this instance, the shaman’s role has not merely been to administer a disruptive drug but to manage and reintegrate the psychological state of the patient so as to ensure the success of the healing ritual.

Similarly, the Native American Church’s ritualistic use of the peyote cactus, which contains the psychoactive alkaloid mescaline, is traditionally facilitated by a shaman, or “Roadman,” who guides worshippers suffering personal/familial crises through all-night prayer ceremonies in a communal tepee. This ancient practice, which is estimated to have been held for up to 40,000 years (Prue 2013), is highly ritualistic, with the initial ingestion of mescaline serving to render worshippers more open to a refiguring of maladaptive thought patterns and reinterpretation of their predicament. In the wake of inducing an altered state, the officiant leads participants in drumming, singing, praying, ceremonial tobacco use, the passing around of sacred objects, and symbolic patterns of movement around the tepee—all intended to foster a sense of transformation (Bergman 1971; Calabrese 1997). In the 1970s, American physician Robert Bergman ethnographically observed Navajo peyote use, noting the indispensable role of Roadman healers who “are trained to look after people who become excessively withdrawn...if a participant begins to stare fixedly into the fire and seems unaware of the others, the road man will speak to him and, if necessary, go to him to pray with him...fan him with an eagle feather fan, splash drops of water on him, and fan cedar incense over him” (Bergman 1971). The administration of the drug is not regarded as healing in and of itself; the therapeutic benefit requires the formation of a mentoring relationship with the healer via ritual (Prue 2013).

Contemporary clinical research has corroborated that, in contrast to using psychedelics as standalone pharmacotherapies, supportive counseling remains a crucial mediating factor (Garcia-Romeu and Richards 2018; Rucker et al. 2018). Mechanistic ingestion of a “pill” is not necessarily enough, and—in fact—may even be contraindicated. Just as general anesthesia is not prescribed for take-home use, but administered under active medical supervision and incorporated within a larger interventional context, safety and efficacy of modern psychedelic therapy seem to be optimized by similar wraparound care (Johnson et al. 2008). As we think about how to bring these treatments above-ground in an era defined by anxiety, despair, loneliness, and alienation (Case and Deaton 2020), it is constructive to imagine how mental healthcare systems might practically evolve in the future. Such an exercise seems even more crucial in the throes of a pandemic whose traumas will demand more of mental health services in years to come (Vahratian et al. 2021).

Institutional parameters of the biomedical model will *ipso facto* limit how modern-day psychedelic treatment is implemented, at least initially (Johnson et al. 2008; Sessa 2005; 2016). However, one obvious question is whether Western medicine can draw upon indigenous knowledge as it integrates psychedelics into current clinical environments. It would, for instance, seem critical for health systems to preserve the ancient ritualistic elements of psychedelic-based therapies, with close attention to assessment, set and setting, time for preparation, processing and dialogue, and re-integration after profound experiences, as commonly practiced in current clinical research (Carhart-Harris et al. 2018; Garcia-Romeu and Richards 2018). Whereas studies increasingly show that a compound like ketamine may be effective when administered in standard clinical infusions (Corrigger and Pickering 2019), interventions using psilocybin and MDMA have been most effective when carried out over several weeks with oversight from therapists (Carhart-Harris et al., 2021; Davis et al. 2020; Griffiths et al. 2016; Mitchell et al. 2021). Some might ask whether society is willing to invest in such resource-intensive treatments—activities for which entire days/weeks were often devoted by our ancient forebears. And if so, can such interventions exist at scale within a capitalist system that often diminishes flexibility in working peoples’ lives and severely strains the clinical time healers may spend with their patients? Given our growing mental health crises, it may be more apropos to ask whether we can afford to maintain an ineffectual status quo in current healthcare systems that often place profits over people.

In addition to logistical considerations, it is also worthwhile to think about clinical settings that may stand to gain most from incorporating psychedelic treatments. Research suggests a clear fit within addiction treatment and psychiatric care for people with mood or anxiety disorders, as well as facilities specializing in cancer treatment and hospice or palliative care. Could we imagine deploying psychedelics in assisted-living facilities? (George and Hanson 2019). For rehabilitation of incarcerated or formally incarcerated individuals? (Doblin 1998; Hendricks et al. 2018; Leary 1969).

Looking forward, psychedelic therapists will require systematic training and licensing consistent with our education/certification of other health professionals (Nutt and Carhart-Harris 2021; Phelps 2017). Given that an aspect of shamanic power has been the intimate “embeddedness” of the figure within the social relations of discrete human groups, it will be critical to train modern practitioners who reflect local populations and to set up equitable, culturally-sensitive treatment networks in urban and rural environments accessible to people across class, racial, gender, ethnic, and generational boundaries (i.e., not just available to a wealthy metropolitan elite) (Thrus and Garcia-Romeu 2021). How might practitioners exist as part of healthcare teams, and how accommodating will frontline professionals and funders be?

There is a long way to go in answering these and other questions, and, as recent history teaches, any paradigm-shifting will likely face major cultural and political-economic resistance (Kuhn 1996). But engineering a systems that could help those who are hurting pursue the underlying causes of their pain, trauma, and distress—the mechanisms of which remain poorly understood—and enjoy lives as more open, pro-social human beings could have manifold benefits. Patients might emerge from

therapy feeling greater sense of purpose, renewed solidarity and interdependence with others, and unity with a planet destabilized by anthropogenic climate change (Watts et al. 2017). One can imagine those successfully transformed by psychedelic therapy being less disconnected, less psychologically attached to prior internalized pain, less prone to self-harm (e.g., DoD), and less susceptible to the modern-day “altered states” offered by harmful drugs, internet, video games, social media, and mindless consumption. While admittedly speculative in the absence of research-derived findings, it is plausible that therapeutically guiding contemporary humans through psychedelic experiences could potentially serve as a means of provoking new ideas/innovations to push through areas of cultural stagnation, fragmentation, and long-standing geopolitical conflicts. For instance, the Multidisciplinary Association for Psychedelic Studies is currently pursuing psychedelic interventions for conflict resolution between Arabs/Israelis and Catholics/Protestants (Roseman et al. 2021).

It will inevitably be argued that retooling mental health systems is “too expensive”. However, from a health economics perspective, potentially treating underlying causes of distress could reduce co-morbidities and ease burden on inpatient and ambulatory institutions. Moreover, as preliminary psychedelic research has established longitudinal efficacy of *single-dose* treatments (Griffiths et al. 2016; Ross et al. 2016), such an approach could transform current models reliant on long-term use of expensive—and often modestly effective—pharmaceuticals that commonly produce unwanted side effects. Economically, how many person-hours of work annually lost due to depression and related conditions could be recovered? Beyond economics, can we, as our ancestors before us, envision the human value of increased wellbeing, quality of life, insight, and balance and fellow-feeling that psychedelic treatments might engender?

There is much work to be done to bring such a vision to fruition. While there is emerging clinical data—for instance, a robust literature of studies establishing the safety and efficacy of ketamine-assisted treatment for depression (see Salahudeen et al. 2020) as well as increasingly high-quality studies on psilocybin-based therapies for depression (Carhart-Harris, et al. 2021; Davis et al. 2020)—larger and more robust clinical trials are needed. Emergent data will help flesh out best practices for identifying appropriate treatment candidates and proper dosages for different patient groups, optimal regimens for set/setting, and protocols for managing adverse events. Given the ancient nature of psychedelic therapies, there may be particularly important—if unconventional—roles for non-clinical experts (e.g., social scientists, archaeologists, religious studies scholars) in the clinical deployment and evaluation of modern therapies. Moreover, ethicists, philosophers, and other scholars from the social sciences and humanities may also fruitfully explore practical and ethical questions regarding the therapeutic effects of psychedelics as well as more conceptual inquiry (e.g., how the nature of the mind-brain relationship may be clarified or problematized by psychedelic therapy).

Great vigilance will be needed regarding private operators already working to commodify these complex therapies (which have been used carefully, ritualistically, with sacred purpose by humans outside of a market economy for tens of thousands of years) with quick-fix marketing hype. Importantly, increasing focus on

psychedelics must not depoliticize larger political-economic structures that are perpetuating the material conditions actively degrading the physical and mental wellbeing of millions (Schrecker and Bamba 2015; George and Whitehouse 2021), lest psychedelics become a new “opiate of the masses” that merely distract us from rightful dissatisfaction with the systemic injustices and massive disparities in wealth, income, health and other outcomes that define our era.

Ultimately, we believe a twenty-first century “psychedelic renaissance” anchored in the lessons of antiquity can point healthcare systems—and perhaps even society itself—in a direction that is more humane, more attentive to mental health needs, and more materially (and spiritually) supportive of human flourishing and societal/planetary health in an era currently characterized by historic levels of distress and despair.

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Declarations

Conflict of interest AGR serves as a scientific advisor to NeonMind Biosciences and ETHA Natural Botanicals. The other authors report no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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