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Invited review

Psychedelics: Where we are now, why we got here, what we must do

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ABSTRACT

The purpose of this commentary is to provide an introduction to this special issue of Neuropharmacology with a historical perspective of psychedelic drug research, their use in psychiatric disorders, research-restricting regulatory controls, and their recent emergence as potential breakthrough therapies for several brain-related disorders. It begins with the discovery of lysergic acid diethylamide (LSD) and its promising development as a treatment for several types of mental illnesses during the 1940s. This was followed by its abuse and stigmatization in the 1960s that ultimately led to the placement of LSD and other psychedelic drugs into the most restrictively regulated drug schedule of the United States Controlled Substances Act (Schedule I) in 1970 and its international counterparts. These regulatory controls severely constrained development of psychedelic substances and their potential for clinical research in psychiatric disorders. Despite the limitations, there was continued research into brain mechanisms of action for psychedelic drugs with potential clinical applications which began during the 1990s and early 2000s. Finding pathways to accelerate clinical research in psychedelic drug development is supported by the growing body of research findings that are documented throughout this special issue of Neuropharmacology. Accumulated research to date suggests psychedelic drug assisted psychotherapy may emerge as a potential breakthrough treatment for several types of mental illnesses including depression, anxiety, post-traumatic stress disorder, and addiction that are refractory to current evidenced based therapies. This research equally shows promise in advancing the understanding of the brain, brain related functioning, and the consequential effects of untreated brain related diseases that have been implicated in causing and/or exacerbating numerous physical disease state conditions. The authors conclude that more must be done to effectively address mental illnesses and brain related diseases which have become so pervasive, destructive, and whose treatments are becoming increasingly resistant to current evidenced based therapies.

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1. Introduction

The history of psychedelic substance use, modern research efforts, and their potential clinical applications addressing current treatment resistant mental health disorders evolved through an intriguing and complexly interwoven story linking ancient cultures, modern discovery, pop cultural movements, national and international politics, and well-intentioned laws with unintended consequences. In the context of this history, this commentary discusses the 21st century resurgence of psychedelic drug assisted psychotherapeutic research, the challenges imposed by the United States Controlled Substance Act (US CSA), and the potential for development of medicinal products for the treatment of persisting mental health disorders.

The unrelenting persistence of behavioral disorders, for which those who are afflicted and refractory to current evidenced based therapies, reveal a powerful incentivizing force for advancing new medicinally assisted psychotherapeutic treatments. On the other hand, we enter the 21st century humbled by the daunting challenge of developing medicines for central nervous system (CNS) disorders in response to the failure of so many seemingly promising medicines that emerged from years of clinical trials, billions of US dollars invested, with benefit to risk profiles which at the time, were acceptable to regulatory agencies in the US and globally (Hyman, 2012; Pangalos et al., 2007; Pankevich et al., 2014). With these considerations in mind, the present commentary is not postured as advocacy for a simple or certain solution to the challenges posed by mental health disorders or "brain diseases." Nonetheless, it suggests that pressing public health challenges involving behavioral disorders may be addressed in part by recent advances in neuropharmacology, on the effects, mechanisms of action, and potential clinical applications of psychedelic drugs discussed in this special issue of Neuropharmacology. Together, these advances support our conclusion that increased scientific investigation of psychedelic substances for potential clinical application merits serious consideration among the many other efforts that are vigorously being pursued to address mental health illnesses that continue to be so pervasive in the United States and globally.

The purpose of this commentary is to provide a brief historical context for psychedelic drug research, its modern rise, fall, reemergence, and the importance of finding pathways through the complex legal, policy, and social barriers, to effectively research the battery of potential medicinal applications that may lead to US and international regulatory approval where they may find their place in service to humanity. This story is multifaceted and a thorough elucidation goes far beyond the scope of any commentary, however, the authors have endeavored to provide key references for readers interested in pursuing these diverse issues for further inquiry. We recognized the opinions of researchers, clinicians, policy makers, regulatory agencies, research funders, those views that span culturally across society, and ultimately the legislative halls that govern this nation and those of others. All vary widely, and all merit consideration. The following is our perspective.

1.1. The modern rise of psychedelic drug research and clinical application

Plants and plant-derived substances known to produce psychedelic effects have been used for millennia for their apparent healing powers, in rituals, and for pleasure (Hofmann, 1980; Multidisciplinary Association for Psychedelic Studies, 2007; Nichols, 2004; Strassman, 1995). These have included certain mushrooms, herbs such as nutmeg, anticholinergic plant derivatives, cannabis, and numerous other substances used in medicine, as well as prototypic substances of abuse and dependence such as alcohol, opioids, stimulants and tobacco. Although the apparent reasons for early use must be surmised in the context of archeological investigations and historical records, the reasons and occasions for use included ceremonial, medicinal, and what today might be termed in relation to modern western culture, recreational use. This history is intriguing and has been recounted elsewhere (Bastiaans, 1983; Hofmann, 1980; Merlin, 2003; Multidisciplinary Association for Psychedelic Studies, 2007; Siegel, 1989; University of Maryland, 2013a, b).

The modern era of research and potential clinical development of such substances for treating mental and behavioral disorders was launched by the discovery of a new chemical entity, lysergic acid diethyl amide (LSD) as discussed in the preface and elsewhere in this special issue (Hofmann, 1980; University of Maryland, 2013a). Although discovered in 1938, its potentially powerful effects to alter mood and cognition were not realized until the self-experiment by its inventor, Albert Hofmann, a Sandoz pharmaceutical company chemist, in 1943 on a day that later came to be renowned internationally as Bicycle Day (Tables 1 and 2). Following several years of active research, the first European clinical study was published in 1947; and in 1949, two American psychiatrists, Max Rinkel and Nick Bercel personally brought Sandoz's LSD into the US to begin testing it. Importantly, it was the Federal Food, Drug, and Cosmetic Act (Federal FD&C Act) of 1938 that permitted Sandoz to distribute LSD samples, under the brand name Delysid for investigational research. These samples were given to experts who were believed to have the necessary training and experience to administer such drugs to patients, thereby further evaluating their potential clinical benefits and safety risks (Bonson, 2017). It was heralded in the medical literature and popular press with great promise for the treatment of a variety of serious mental health disorders including anxiety, depression, schizophrenia, war time stress reactions, alcoholism and other substance use disorders (Hofmann, 1980). Its clinically documented favorable safety profile, potency, and its ability to produce powerful and occasionally enduring beneficial psychological effects, led many prominent leaders in the behavioral science field along with the pharmaceutical industry to view LSD, and possibly related chemical entities, as potential breakthroughs in many areas of mental illness, including various forms of drug addiction.

The promise of LSD, psilocybin, mescaline and other psychedelic substances as tools in psychiatric investigation and their

potential for medicinal application was pursued vigorously by many leading researchers in psychiatry and the emerging fields of neuropharmacology and neuropsychopharmacology (Abramson et al., 1955; Freedman, 1968, 1986, 1992; Grinspoon and Bakalar, 1979; Multidisciplinary Association for Psychedelic Studies, 2007; Nichols, 2004; Nutt et al., 2013; Siegel and West, 1975). This area of pharmaceutical research exploration coincided simultaneously with the rapid advancement of research on medicines to treat anxiety, depression and psychosis during the 1950s, which were also essential in the development of the modern fields of psychopharmacology and neuropharmacology (Ban, 2006, 2007; Lopez-Munoz et al., 2011; Stolerman, 2010). The apparent benefits of medicines for such diverse and formerly all too often intractable disorders certainly fueled the hope for LSD and possibly other psychedelics, which were initially referred to the more general term of psychotomimetics, for their ability to produce transient psychotic like states, and equally psychotherapeutic for their ability to relieve such states. Research funding came by way of pharmaceutical companies, institutions such as the US National Institute of Mental Health (NIMH), and importantly, though controversially, from military and intelligence agencies (Kamienski, 2016; Lee and Shlain, 1992; Multidisciplinary Association for Psychedelic Studies, 2007) which appeared to have interests not only in clinical application but possibly as tools for espionage and warfare.

By the early 1960s, research on psychotherapeutic agents including psychedelics contributed to the emergence of new research societies such as the American College of Neuropsychopharmacology, the American Psychological Association's Psychopharmacology and Substance Abuse Division 28, the Behavioral Pharmacology Society, and many others. Even though there was this extensive growing body of clinical research on hallucinogens, especially with LSD, which at the time was being distributed in the US for investigational purposes, there was still no federal legal requirement in the Federal FD&C Act of 1938 requiring pharmaceutical manufacturers to demonstrate proof of clinical efficacy through adequate and well controlled clinical trials. It was on October 10th, 1962, in response to the thalidomide tragedy where children were born with serious birth defects from mothers consuming the drug thalidomide for morning sickness, that the Kefauver-Harris Drug Amendments to the Federal FD&C Act, known officially as the "Drug Amendments of 1962" was signed into public law (Chhabra et al., 2005; Meadows, 2006). This crucial legislation significantly strengthened the FDA's regulatory controls on the experimentation of new chemical entities in humans.

For any new drug substance, pharmaceutical companies were now required to submit as part of their New Drug Application (NDA) adequate and well-controlled studies, demonstrating their drug was both safe and effective for the clinical indication(s) the company was seeking to market. Additionally, there would be the requirement for informed consent of patients before their participation in any clinical trials; adverse drug reaction reports were now going to be required by the FDA; good manufacturing practices would be formalized; and lastly, prescription drug advertising would be transferred from the Federal Trade Commission to the FDA. As a crucial component of the Kefauver-Harris Drug Amendments, the Drug Efficacy Study Implementation (DESI) was initiated, and in 1966, the FDA contracted with the National Academy of Sciences National Research Council to undertake an evaluation of all drugs approved between 1938 and 1962 for clinical efficacy. It would take almost 20 years, 1984, to evaluate and issue final regulatory actions on 3443 marketed drug products, totaling more than 16,000 therapeutic efficacy claims. Of those 3443 drug products, 2225 were found to be effective, 1051 were found ineffective, and 167 were still pending more research. The 1051 ineffective drug products were designated DESI drugs, and with the passage of the Omnibus Budget Reconciliation Act of 1981, reimbursement for DESI drugs was prohibited by Medicaid programs as well as under Medicare Part B (Chhabra et al., 2005; Meadows, 2006; Navarro, 2009).

1.2. The US Controlled Substances Act and the fall of psychedelic drug research

With the implementation of these new regulatory controls following the passage of the Kefauver-Harris Drug Amendments of 1962, Sandoz was equally facing the loss of patent protection for Delysid in 1963. Thus, there was no financial incentive to invest any further in the newly required safety and clinical efficacy studies now needed for regulatory approval as stipulated in the Kefauver-Harris Drug Amendments to the Federal FD&C Act. To complicate matters even more, patterns of abuse were emerging with LSD which included illicit manufacture and distribution (Drug Enforcement Administration, 1995; Hofmann, 1980). LSD was entering popular culture as a "mind-altering" and "mind-enhancing" drug associated with various societal subcultures with a multiplicity of social and political movements including the rise of the "hippie" culture and psychedelia. These social developments contributed to an emerging unfavorable reputation among numerous political and medical leaders (Drug Enforcement Administration, 1995; Hofmann, 1980), and by 1966, Sandoz sought to distance themselves from any research in the US by transferring their remaining supplies of Delysid to NIMH (Bonson, 2017). A summary document by the US Drug Enforcement Administration (DEA) reported that from about 1950 to 1965 "research on LSD and other hallucinogens generated over 1000 scientific papers, several dozen books, and 6 international conferences, and LSD was prescribed as treatment to over 40,000 patients" (Drug Enforcement Administration, 1995). There is little question that the celebrity status garnered by Professor Timothy Leary during this era contributed to both the popular cultural rise of LSD and in turn to its stigmatization and adverse political repercussions by the latter half of the 1960s (Abrahart, 1998; Doblin, 2001; Dyck, 2006; Mansnerus, 1996; The Lancet, 2006).

Along with the emerging so-called "counterculture movement" that embraced LSD and related substances was the increasing adoption of the term "psychedelic" as the general umbrella term for LSD, psilocybin, and numerous other substances (Multidisciplinary Association for Psychedelic Studies, 2007). The encouragement in the use of psychedelics to "Turn on, tune in, and drop out" by Professor Leary (Mansnerus, 1996) may have fueled the emerging divide between political leaders, and those of many young people whose views were in opposition to the Vietnam War, and or active in issues ranging from racial equality, women's rights, to environmental advocacy. Regardless of truth or fault, this complex and rapidly evolving period in the social political landscape contributed to political backlash. Certain aspects of the design and content of the 1970 US Controlled Substances Act (CSA) (Table 3) codified harsh penalties for manufacture, possession, and use of many psychedelics, which hindered their research and medicinal development (Abrahart, 1998; Doblin, 2001; Dyck, 2006; Mansnerus, 1996; Multidisciplinary Association for Psychedelic Studies, 2007; The Lancet, 2006).

This stark characterization of LSD and related psychedelic substances firmly took root and contributed to an era of misinformation, politicization, and irrational fear by many in society, subsequently causing the political leadership on both sides of the aisle to collectively take action, which resulted in the near banning of clinical research with these substances. Time magazine's description of the banning of LSD and other psychedelic substances by several states in 1966 summarized how these substances

Table 1
Bicycle Day: Albert Hofmann's personal discovery of the diverse psychopharmacological effects of LSD.

Bicycle Day commemorates the day, April 19, 1943, when chemist Albert Hofmann intentionally ingested 250 μg of LSD in his laboratory at the Sandoz pharmaceutical company in Basel, Switzerland. The commemoration of Bicycle Day originated in DeKalb, Illinois in 1985, when Thomas B. Roberts, then a Professor at Northern Illinois University, founded the first Bicycle Day as a personal celebration at his home. Several years later, he distributed announcements to publicize the idea of an annual celebration commemorating Hofmann's intentional exposure with LSD.

Table 2
The discovery and seminal LSD experiment by Albert Hofmann.

Albert Hofmann discovered LSD in 1938, while researching various substances derived from a fungus ergot which was known to produce hallucinations but also considered to have potential clinical applications. He synthesized the chemical and it was tested in routine animal studies that apparently did not suggest at the time a profile for potential medicinal application (Hofmann, 1980). He set aside this substance and did not return to it until 1943 when he accidently ingested an apparently trace amount of the substance. It led to some intriguing psychological effects that reminded him of some childhood experiences. He decided to investigate further in the then not uncommon practice of self-experimentation to document the nature and time-course of the effects. He recounted the experience through his laboratory notes in his 1980 book, "LSD — My Problem Child". On Friday, April 19th, at 4pm he intentionally ingested 250 μg of LSD. By 5pm he began to experience symptoms including dizziness, anxiety, paralysis, visual distortions and a deep desire to laugh. This led to more intense symptoms that were increasingly disturbing and disrupting to his thinking and he asked his assistant to accompany him home where they rode bicycles because of the wartime restrictions on automobile use.
Upon arrival at his home, he asked his assistant to summon his family doctor and to request milk from a neighbor for consumption as a potential antidote. From about 6 to 8:00 p.m. the effects were the most intense and he felt terrified, fearful for his life, and delusional. When his doctor arrived, he was beginning to feel better with the emergence of somewhat more pleasant feelings with kaleidoscopic colors and images that were more positive than negative. His doctor determined that his pulse, blood pressure, and breathing were normal but that his pupils were extremely dilated. Upon waking the next morning, he felt a sense of well-being, pleasure with life, and deeper appreciation for the beauty of the world about him. Future experiences were considered by Hofmann as enhancing to his life and thinking (Hofmann, 1980; University of Maryland, 2013a).

became widely perceived: "*Within hours of each other last week, the Governors of California and Nevada signed bills imposing fines of as much as $1000 and sentences of up to one year behind bars for possession of the hallucinogenic drug LSD. This week a similar measure is expected to become law in New Jersey. In the weird light of LSD's often nightmarish effects, it might seem that such a crackdown would be widely applauded. On the contrary, U.S. legislators and drug experts are actually engaged in a strenuous debate over the degree and kind of controls that should be imposed on LSD.*"

The CSA emerged along with other international drug control treaties that included, the international "Single Drug Convention" of 1961, the "Psychotropic Convention" of 1971, and other efforts from nations to harmonize their drug regulatory frameworks (International Narcotics Control Board, 1994; National Academies of Sciences, 2017; Spillane and McAllister, 2003). These national and international drug control structures were intended to protect the broader public health, and although there have been noted benefits, there have also been inadvertent consequences and deficiencies that in turn led to new treaties internationally, with new laws and legal interpretations at the national and international level (Sinha, 2001; Spillane and McAllister, 2003; Spillane, 2004; Transnational Institute, 2006). Without challenging the appropriate need and application of the Schedule I designation for certain substances (Table 4), it must also be acknowledged that historical cultural and religious practices going back several centuries were also adversely impacted (Table 5).

Regardless of the general public health intent and benefits, the CSA, as was intended, severely restricted research on substances placed in Schedule I. Schedule I substances are defined in the CSA by three factors: *(A) The drug or other substance has a high potential for abuse; (B) The drug or other substance has no currently accepted medical use in treatment in the United States; (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision*. The law does not outright ban research on Schedule I substances but it includes restrictions and significant barriers and requirements that discourage scientists and clinicians from attempting to conduct research on Schedule I substances or even applying for funding for such research (Howell, 2017; Woodworth, 2011). There is growing recognition in the US and other countries for the need to reduce barriers in researching drugs placed in Schedule I in the US and its equivalent class in other nations. An example of a regulatory hurdle imposed by the CSA and how it was implemented was the exceptional burden that a potential researcher would need to independently submit study proposals to both the FDA and a US Public Health Service (PHS) board, adding potentially months of time and effort to be able to conduct research on marijuana (Ingraham, 2015). In 2015, the US Department of Health and Human Services (DHHS) changed its formal guidance on procedures for providing marijuana for research by eliminating the need for the US PHS review, thus eliminating one of many such obstacles (Ingraham, 2016; US Department of Health and Human Services, 2015). The 2015 DHHS action only addressed marijuana and left other potentially modifiable barriers in place but it is an example of progress in this area. To identify additional approaches to support and expedite research on Schedule I substances, a special symposium was convened at the annual meeting of the College on Problems of Drug Dependence in June, 2017, in which representatives from leading research organizations, along with the DEA, FDA, and NIDA, discussed the challenges and adverse consequences of the barriers to Schedule I drug research and what might be done to facilitate such research (Howell, 2017).

1.3. Twenty-first century psychedelic drug research and development: a new era

Today, there appears to be rapidly growing awareness, anticipation, and hope for the potential of several psychedelic drugs to become medically approved for various psychiatric disorders as discussed further in this article and elsewhere in this special issue (Carhart-Harris et al., 2016; Chabrol, 2013; Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Hartogsohn, 2017; Krebs and Johansen, 2012; Langlitz, 2012; Mithoefer et al., 2011; Multidisciplinary Association for Psychedelic Studies, 2017c; Pisano et al., 2017; Oehen et al., 2013; Sewell et al., 2006). Psychedelic medication development efforts began to accelerate following the 1990s, when new generations of behavioral health researchers began an in-depth reexamination and rediscovery of potential uses these substances might hold by applying state of the art clinical research development approaches, methods, and procedures. For many in this field of investigation, the new marshaling of interest is essential to better understand the brain and mechanisms of drug

Table 3
The US Controlled Substances Act and psychedelic drug regulation in the United States.

The Controlled Substances Act (CSA) was established during the administration of President Richard Nixon in 1970, during the same time that the International Psychotropic Convention of the United Nations of 1971 was being developed. Many of the provisions of the CSA and the Psychotropic Convention were thus in harmony (see more specifics concerning the Psychotropic Convention in United Nations, 1971) (United Nations, 1971). In brief, the CSA is a federal law that regulates the manufacture and distribution of substances and medicines, designated as "controlled substances", on the assumption that they require special controls due to their potential known or predicted (in the case of new substances and medicines) risks of abuse and addiction.
The nature and extent of the controls varies widely as a function of the presumed nature and severity of the risks and whether the substance is the active ingredient in a product approved for medicinal use by the Food and Drug Administration (FDA). Substances not approved for medicinal use are placed (also referred to as being "listed" or "scheduled") in Schedule I ("CI"), regardless of the extent and nature of their abuse-related risks. Substances approved as prescription medicines are placed in Schedule II through V ("CII – CV") (See Table 4).
For approved prescription medicines, the schedule placement is intended to be commensurate with the known or predicted risks of the substance as determined by an analysis of 8 factors of the CSA (See Table 6). This provides for a comprehensive evaluation of the pharmacology, abuse potential, history of the substance and related substances, public health impact, physiological and psychological dependence, and whether the chemical has been previously scheduled, in which case the new medicine is placed in the same schedule with very few exceptions (Calderon et al., 2017; Drug Enforcement Administration, 2017; U.S. Food and Drug Administration, 2017a).
During the time the CSA was being developed, several states had banned the possession and use of substances then increasingly referred to as psychedelics and there was concern by many political leaders about the effects and use of these substances. Thus, despite questions about their actual risks of abuse, physical and psychological dependence, they were placed in Schedule I. Final drug scheduling decisions for substances evaluated since the original scheduling that was included in the 1970 CSA are completed by the Drug Enforcement Agency (DEA), with input from the Department of Health and Human Service's FDA and National Institute on Drug Abuse (NIDA). This dual agency approach was a compromise by those in President Nixon's administration, some of whom argued that scheduling should be a legal matter and some who argued that it should be primarily guided by a scientific medical perspective. Changing the schedule of a substance or product and removal from the CSA altogether involves a complicated process by the DEA, FDA and NIDA (Drug Enforcement Administration, 2017; National Academies of Sciences, 2017; Spillane and McAllister, 2003; U.S. Food and Drug Administration, 2017a).

action as well as to address challenging mental health related disorders that are refractory to current evidence based treatments in the US and globally (Office of Disease Prevention and Health Promotion, 2017; World Health Organization, 2013).

Remarkably, in the context of 20th century history, one particular Schedule I substance, 3,4-methylenedioxymethamphetamine (MDMA), also known as "ecstasy", was granted a Breakthrough Therapy Designation as an MDMA-assisted psychotherapy Investigational New Drug Application (IND) for post-traumatic stress disorder (PTSD), with FDA agreeing to a special protocol assessment that could expedite phase 3 clinical efficacy trials (Dean, 2017; Multidisciplinary Association for Psychedelic Studies, 2017a). Following completion of those clinical trials, the data must be submitted to the FDA as part of an in-depth scientific regulatory review process. If the FDA, upon review of the compiled clinical data, concludes there continues to be an acceptable margin of safety for patients as well as MDMA being validated to be statistically efficacious, there is the potential MDMA may be submitted for regulatory approval as a NDA in the treatment of PTSD (Multidisciplinary Association for Psychedelic Studies, 2017a) (Table 6).

It is impossible to predict what advances in the understanding of brain function, brain diseases, and medicine based treatments would currently be available had psychedelic research continued unhindered and expanded during the past half-century instead of being abruptly deterred nationally and globally during the 1970s. Dwelling on opportunity lost is not the purpose of this article for this special issue of Neuropharmacology, however, a review of the current state of mental illness in the United States illustrates why it is imperative to accelerate psychedelic drug research to determine its potential as new treatment options for people whose mental health disorders are refractory to current evidence based treatment modalities.

2. Public health need

The public health need for new medicinal treatments to support those who find available medicines ineffective or unacceptable due to side-effects, compliance, and cost demands are vast (Office of Disease Prevention and Health Promotion, 2017; World Health Organization, 2013). Unfortunately, the pipeline for new medications is relatively small given the scope of mental health problems and the fact many major pharmaceutical companies that formerly pursued aggressive and very expensive research in this field have withdrawn, or at least significantly scaled back their efforts because of the high rate of failure to find medications that are acceptable for approval, given the often small and uncertain magnitude of benefit, along with discouraging side-effect profiles (Wegener and Rujescu, 2013). Large risk-averse companies may be waiting for smaller firms and consortiums to advance the development of psychedelics before attempting to purchase the rights, partner, or develop competing products. Present development of psilocybin for severe depression and anxiety related disorders and MDMA for PTSD are currently being shepherded by small organizations that may not have the full funding to develop the medicines through the expensive labyrinth of safety studies and large-scale phase 3 clinical efficacy trials (Carhart-Harris et al., 2016; Emerson et al., 2016).

The research emerging from these programs may be as important from the perspective of what is being learned about the brain and its disorders as it is to potentially offering true breakthroughs in psychotherapeutics. For example, whereas anxiolytics and antidepressants are typically taken every day, and often for years to manage symptoms, in the case of psilocybin, a single medication assisted psychotherapeutic session has been demonstrated to reduce severe symptoms of ostensibly intractable anxiety and depression for more than one year (Carhart-Harris et al., 2016). Similarly, one or two MDMA-assisted psychotherapeutic sessions appear to produce strong and persisting symptom reduction and quality of life enhancement in persons who had been diagnosed with PTSD (Mithoefer et al., 2011). Such lasting benefits aided by one to two doses of a medication, particularly in severely ill and debilitated patients, may emerge as one of the most momentous breakthroughs in psychiatry and medication development in decades. What is learned in these endeavors may lead to the knowledge that makes possible the necessary advancement in adjacent areas of development (Pollan, 2015; Slater, 2012).

There are many barriers to the development of psychedelic and other nontraditional therapies that include their histories of abuse and societal concerns and, in some cases, challenges for patent protection which may deter large investors. Fortunately, the FDA has mechanisms that can enable seriously ill individuals who are refractory to all recognized medically acceptable clinical therapies to be treated with medications that have not yet been approved. These

Table 4
The following are the drug control schedules of the US CSA, along with examples of substance placement ("scheduling" or "listing").

Internationally, signatories to the international drug control convention have their own controlled substance scheduling frameworks which are generally harmonized with one another, however, the scheduling scheme through the CSA provides an exemplary model (Spillane and McAllister, 2003).
Schedule I (C-I): Substances that do not have an accepted medical use and have a high abuse potential and/or were designated for C-I in the 1970 CSA, e.g., heroin, GHB, "bath salts", LSD, DMT, psilocybin, mescaline, cannabis. Note, "high abuse potential" is not defined and in practice means sufficient abuse potential to warrant scheduling thus C-I listed substances vary widely in their actual abuse potential. Nonetheless, penalties for possession, manufacture and use can be significant. Special DEA licenses and other requirements are required for research and have proven sufficiently arduous that research on these substances has been extremely limited (Nutt, 2015; Nutt et al., 2013; Scientific American, 2014).
Schedules II-V: Substances (drugs) that have an accepted medical use (typically approved for medical use by the FDA). C-II is for substances with the highest abuse and physical dependence potential and overall risk characterization; C-V is for substances with the lowest abuse potential and lowest dependence potential and risk (Scientific American, 2014).
C-II includes oxycodone, hydrocodone, phencyclidine, morphine, amphetamine, pentobarbital, methadone. C-III includes buprenorphine, secobarbital, dronabinol, chlorphentermine. C-IV includes tramadol, diazepam, phenobarbital, mazindol, pentazocine, sibutramine, butorphanol. C-V includes low dose codeine, lacosamide, pregabalin.

Table 5
Schedule I placement of psychedelic substances in the US CSA clash with historical cultural and religious practices.

Using archeological and historical records as a reflective guide confirms the ordinary custom of incorporating psychedelics as part of ceremonial religious healing practices which date back centuries to thousands of years. North American Indians have been integrating the use of psychedelics such as peyote, which contains the psychedelic substance mescaline, for hundreds of years in their ceremonial religious traditions for healing (Traditional Indian religious use of peyote,1996; Halpern et al., 2005; Parker, 2013; Swan, 2009). Also incorporated in ceremonial traditions has been the use of psilocybin containing mushrooms (Metzner, 1998). South American shamans and other cultures have combined a number of indigenous plants to create a ceremonial drink, more commonly known as "ayahuasca." Ayahuasca contains a combination of DMT, a naturally occurring alkaloid found in most living species, and a Monoamine Oxidase Inhibitor (MAOI) which inhibits an enzyme (MAO) found in the human body, thus preventing DMT from metabolism (Riba et al., 2003). DMT retains its active oral form through the inhibition of MAO, thus giving rise to a psychedelic experience which is considered essential to those shamanic based healing ceremonies (McKenna et al., 1998; Riba et al., 2003; Tupper, 2008).
As recently as 2006, the US Supreme Court case *Alberto R. Gonzales, Attorney General,* et al., *Petitioners v. O Centro Espirita Beneficente Uniao do* Vegetal et al (2006), concluded in an 8-0 ruling that the religious organization O Centro Espirita Beneficente Uniao do Vegetal (UDV) who incorporate hoasca tea, also known as ayahuasca, into their ceremonial religious practice, were legally protected under the 1993 Religious Freedom Restoration Act established by Congress. The US Supreme Court's ruling in favor of UDV effectively prevented the application and enforcement of the CSA's Schedule I status when it came to the use of these substances in faith-based organizations' religious healing ceremonies (Küfner et al., 2007). Thus, there appears to be a variance where modern legal precedent establishes a Constitutional protected use of these substances as part of faith-based organizations' religious healing ceremonies. Simultaneously, the nation's medical community, who seeks to conduct scientific clinical research for potential therapeutic treatment indications for mental and behavioral health disorders, continues to be impeded.
This incongruity of US laws suggests the need for constructive policy deliberations to reconcile this difference. A political discourse at the national level may ultimately be required to resolve what some may argue as an unfortunate bias where faith-based religious organizations and the medical community are both equally seeking, albeit through different settings, the healing potential behind these substances. A logical outcome would include an equal defense of the medical community's legitimate interest in seeking the truth through science by pursuing research that can validate potential therapeutic application of these substances. The nature of this nation's mental health crisis is such that subscribing to the status quo out of legacy fear is self-evidently unacceptable. Fear impedes the necessary innovative, methodical, and scientifically based clinical research trials that would answer the battery of multi-decade old questions surrounding the potential clinical uses for such substances in psychedelic-assisted psychotherapy, and in turn may equally validate their historical use in faith-based religious healing ceremonies.

are called Expanded Access programs or otherwise known as "compassionate use programs" that can provide access to experimental drugs under the umbrella of an IND for patients who may not qualify for participation in a clinical trial but who give consent to accepting the risks for the opportunity to receive the drug. In being accepted as part of an IND, patients are informed of the uncertainties and risks of such drugs and treatment modalities (Calderon et al., 2017; U.S. Food and Drug Administration, 2016a, 2017b). These programs are crucial because there are numerous individuals whose mental health disorders do not adequately respond to currently approved FDA medicines for the indications in which they were studied. Expanded access programs serve the humanitarian purpose of providing patients with no other acceptable recourse to willfully try a treatment with uncertain risks and benefits, as well as to enable the collection of clinical data through their participation that may help learn more about the potential effects, benefits and risks of the drug. Such programs and efforts might be increasingly utilized to apply and evaluate promising psychedelic substances being evaluated as potential new medicines.

3. Summary of major mental health challenges facing the United States

The United States confronts today a mental health crisis that by many measures is not contracting; instead, it is expanding (Case and Deaton, 2015; Center for Behavioral Health Statistics and Quality, 2016; Centers for Disease Control and Prevention, 2014; Higgins, 2017; Kochanek et al., 2016; National Drug Intelligence Center, 2011; Rudd et al., 2016; Sacks et al., 2015; Stahre et al., 2014; U.S. Department of Health and Human Services Office of the Surgeon General, 2016; Volkow, 2014). Furthermore, the overwhelming scope of this crisis is one where mental health disorders both grossly invade as well as subtly infiltrate the foundational fabric that comprises, sustains, and enterprises this nation, its citizenry. The multi decade long erosion in our nation's overall state of mental health (U.S. Department of Health and Human Services Office of the Surgeon General, 2016) and our inability to sustainably alter the trajectory in treating mental health disorders such as treatment resistant depression, anxiety, addiction, and PTSD, has resulted in a steady-state depletion of our nation's internal intellectual, innovative, and economic capacity (Centers for Disease Control and Prevention, 2013; Florida Council for Community Mental Health, 2007; Insel, 2015; Kessler et al., 2008; Pal, 2015).

Continued decline in mental health poses an existential strategic threat within the United States whose impact is now being fully recognized (West, 2016). Our nation's economy hinges squarely on energetic pioneering competitive businesses whose foundation depends upon the people who sustain them. Mental

Table 6
Multidisciplinary Association for Psychedelic Studies (MAPS) (Multidisciplinary Association for Psychedelic Studies, 2017b).

The Multidisciplinary Association for Psychedelic Studies (MAPS) was founded in 1986 by Rick Doblin as a non-profit research and educational organization whose mission is to develop "medical, legal, and cultural contexts for people to benefit from the careful uses of psychedelics and marijuana." Specific efforts include:
- Researching psychedelics and marijuana for potential development into prescription medicines.
- Training therapists and working to establish a network of clinical treatment centers.
- Supporting scientific research into neuroscience, creativity, and spirituality.
- Educating the public at large about the potential risks and benefits from psychedelic and marijuana use.
- Ongoing research for the development of psychedelic substances for the treatment of mental health disorders include the following:
  - MDMA-assisted psychotherapy for post-traumatic stress disorder (PTSD), autistic adults with social anxiety, and individuals with anxiety related to life-threatening illnesses.
  - Medicinal cannabis for a variety of disorders including symptoms of posttraumatic stress disorder (PTSD) for veterans of war.
  - LSD-assisted psychotherapy for anxiety and other mental health disorders.
  - Ibogaine-assisted treatment for substance abuse disorders.

health disorders know no boundaries; they cross-cut all demographics; they spare no socioeconomic class; they permeate all cultures; and they inflict their debilitating effects on workers and by extension their families, from the service sector, to the manufacturing sector, to the professional sector. The people who suffer mental health disorders are the same persons who make-up the economic vitality of our business community and yet simultaneously are the consumers whom businesses depend upon to buy their products and services. Moreover, our nation's mental health crisis contributes directly to exacerbating disease state crises, where our nation's healthcare has become increasingly reactionary. Given the data demonstrating the extensive involvement of mental health disorders such as depression contributing to the etiology of numerous disease states such as asthma, arthritis, cardiovascular disease, cancer, diabetes, and obesity, addressing mental health illnesses is proving essential in the course corrections necessary to positively affect treatment outcomes for such chronic diseases (Chapman et al., 2005).

The US Federal Government, along with partnering state governments, local municipalities, combined with the battery of public and private partners, have endeavored to stem this erosion of mental health through implementing numerous national policy and regulatory initiatives in addition to supporting mental health prevention and treatment programs over the years (Mental Health America, 2017; National Alliance on Mental Illness, 2017; National Institute of Mental Health (U.S.), 2017; The Pew Charitable Trusts and John D. and Catherine T. MacArthur Foundation, 2015). Although these efforts continue to impact this crisis, the enormity is such that the trajectory remains disappointingly to many leaders who call for stronger actions (American Psychiatric Association, 2015). Table 7 provides examples of the diversity and magnitude of mental health related challenges in the United States. Although there are regional differences as well as globally, the situation in the United States is similar in many respects to that of other nations (World Health Organization, 2001, 2017).

To date, our mental health prevention and treatment programs, including regulatory and policy initiatives, collectively have not decreased the trajectory for a battery of mental health disorders being reported annually. On the contrary, they continue to increase over the time periods where data continues to be collected (Higgins, 2017). It can be argued everything possible that can be done is being done, and it can be equally argued that everything possible has not been done. Significant distress is continuously expressed from all stakeholders, including government executive civilian and military leadership, the broader medical community, and the full span of leadership across the business community, as to the long-term effects from an unhindered national mental health crisis. This is most recently evidenced by the establishment of the *President's Commission on Combating Drug Addiction and the Opioid Crisis*. On October 26, 2017, following the recommendations from the Commission's interim report (President's Commission on Combating Drug Addiction and the Opioid Crisis, 2017), the President declared a Nationwide Public Health Emergency to combat the opioid crisis (The White HouseOffice of the Press Secretary, 2017). Earlier in the year on April 19, 2017, the DHHS announced their strategy for fighting the opioid crisis during the National Rx Drug Abuse and Heroin Summit (Price, 2017). These declarations follow the *2016 Surgeon General's Report on Alcohol, Drugs, and Health* (U.S. Department of Health and Human Services Office of the Surgeon General, 2016), and the bi-partisan legislation passed during the 114th United States Congress, known as the *21st Century Cures Act*, which incorporated numerous significant national public health policy reform provisions (U.S. Congress, 2016).

3.1. Cumulative behavioral healthcare and societal costs

The NIMH estimates the total costs associated with serious mental illness, those disorders that are severely debilitating and affect about 6 percent of the adult population, to be in excess of $300 billion per year (National Institute of Mental Health (U.S.), n.d.-a). Related to substance use disorders, the National Institutes of Health (NIH) documented that in 2013, 16.5 million Americans reported heavy drinking of alcohol; 55.8 million were current cigarette smokers; and 24.6 million were current illicit drug users. Abuse of tobacco, alcohol, and illicit drugs are estimated at approximately 740 billion US dollars in costs related to crime, lost work productivity and health care (National Institute on Drug Abuse, 2017; West, 2016). The costs related to these disorders and pressure on local, state and federal budgets are staggering and continue to challenge existing health care approaches (Centers for Disease Control and Prevention, 2017; The Pew Charitable Trusts and John D. and Catherine T. MacArthur Foundation, 2016).

3.2. Stigmatizing scientific medical problem solving

The challenges of preventing, diagnosing, and treating mental health disorders are increased by social issues and stigmatization that often hinders self-disclosure and help-seeking by those afflicted, including their families (Corrigan et al., 2014). Addressing stigma itself is not simple, particularly with respect to addictions where the goal is to facilitate admitting the problems, generating the readiness to seek assistance, and the determination to end them, but never normalizing substance use (Jones, 2007; Koop, 2007; Satel, 2007). This is not to imply that there are simple and effective treatments for all who seek them but addressing stigma for mental illness and addictions is vital. What is also needed is the acknowledgment, willingness, and resolve to expand scientific medical research in areas that display potential long-term material impact in diminishing mental health disorders.

Concerns about stigma may also include patient participation in

certain potential psychedelic drug treatment modalities, which are themselves characterized by decades of culturally established stigmas and histories, where those who might benefit would refuse their use in treatment because of those stigmas. As mentioned earlier and elsewhere in this special issue, psychedelic drugs including, *N*,*N*-Dimethyltryptamine (DMT) (Johnson et al., 2008), psilocybin (Carhart-Harris et al., 2016; Grob et al., 2011; Johnson et al., 2008; Kumar, 2008; Sewell et al., 2006), 3,4,5-Trimethoxyphenethylamine (mescaline) (Johnson et al., 2008), and LSD (Gasser et al., 2014; Johnson et al., 2008; Sewell et al., 2006), continue to elicit significant attention within national and international research communities, for their potential treatment in PTSD, addiction, depression, and anxiety, when used concomitantly in clinically supervised psychotherapy sessions. Although not known as a classical hallucinogenic agent, MDMA (Chabrol, 2013; Grob, 2013; Johnson et al., 2008;Mithoefer, 2011; Oehen et al., 2013), has amassed equal attention for potentially treating some of the same disorders. Media coverage of such research has included well investigated stories that provide compelling accounts of the research and potential benefits, but also eye-catching headlines, and street and club terms, such as “magic mushrooms”, “ecstasy”, and “getting high”, (Hoffman, 2016; Philipps, 2016; Pollan, 2015; Slater, 2012). Whether such media coverage increases or decreases overall stigmatization will remain to be seen but future reporting on scientifically accurate content would constructively contribute to balanced perceptions, discussions, and conclusions.

4. Evolving to address a critical national healthcare need

We are nearly two generations removed from when the CSA and the International Convention on Psychotropic Substances were ratified resulting in formidable barriers to research. Nonetheless, the past two decades have been accompanied by slowly increasing research and the emergence of studies that suggest significant potential for the treatment of a variety of mental disorders using psychedelic containing drugs (Carhart-Harris et al., 2016; Chabrol, 2013; Gasser et al., 2014; Grob et al., 2011; Krebs and Johansen, 2012; Mithoefer et al., 2011; Oehen et al., 2013; Pisano et al., 2017; Sewell et al., 2006). Most of the studies have been relatively small and would be considered phase 1 and phase 2 clinical studies by the FDA (U.S. Food and Drug Administration, 2017d). Thus, substantial, costly additional phase 3 clinical efficacy studies will be required over the course of at least several more years from the time those studies are implemented to support any NDA for approved medicinal use. The FDA regulatory review and approval process will undoubtedly be far more complex than for most medications and will likely involve external advisory committee hearings to advise on approvability, which schedules (e.g., II, III, IV or V) of the CSA the drugs should be placed in, and the evaluation of recommendations for Risk Evaluation and Mitigation Strategies (REMS) (U.S. Food and Drug Administration, 2015, 2016b). The probable post-marketing requirements and restrictions will likely be extensive. However, if the requirements contribute to enabling a path to market for therapeutic applications, with manageable burdens to prescribers and the pharmacies that dispense directly to clinics conducting assisted psychotherapeutic sessions, they could both open the door to appropriate patient access while also requiring the collection of vital additional clinical data that may better guide any potential expansion of use. With increasing clinical knowledge over time that would come with the use of these substances in assisted psychotherapy sessions, emerging information that was previously unknown may result in potential changes in medication labeling which may further contribute to the recognition of public health benefits while simultaneously minimizing potential risks to patients (Brooks, 2014; Dasgupta and Schnoll, 2009; Frame et al., 2013; Johanson et al., 2009; Worthy, 2016).

Research is essential to provide the solid science foundation to identify and address the risks, benefits, and conditions that promote the safe use of psychedelic substances. The scope of the public health needs and challenges in determining if psychedelics drugs will be approved for medicinal use are equally enormous. The research community more than ever seeks to investigate these substances which include how they should be integrated with behavioral and other evidenced based therapies to provide safe and effective interventions for PTSD, addiction, depression, and/or anxiety and possibly other mental health disorders. It will only be through rigorous, methodical and sustainable clinical trials where researchers will be able to legitimately address these critical efficacy questions. Given that our overall current evidence based clinical treatment modalities are not adequately stemming this nation's mental health problems, all options should be actively considered. At the very least, this entire field of research warrants a vigorous scientific, clinical, and policy deliberation from current national and international subject matter experts specializing in this research.

When currently accepted mental health treatment modalities have been demonstratively exhausted such as in this crisis, it's paramount that government, nonprofit, and commercial organizations collectively evolve a willingness to lead in brainstorming innovative paradigm shifting treatment endeavors. This willingness to branch into untapped research areas is critical, even if the proposed treatment endeavors appear to run counter to firmly established cultural norms or cherished ideologies. Today, there exists a historical record with examples of impeding out-of-the-box problem solving in areas of science, medicine, and philosophy. Moreover, it is legacy fear that often thwarts many attempts to counter sufficiently time-honored belief systems, and there is modern precedent sticking with the status quo. When there is a choice

Table 7
Examples of major 21st mental health challenges in the United States that potentially may be addressed in part by innovative clinical therapies including medications derived from or analogs to certain psychedelic substances (see elsewhere in this special issue).

Major Depressive Episodes	In 2014, an estimated 15.7 million adults aged 18 or older in the United States had at least one major depressive episode in the past year (National Institute of Mental Health (U.S.), n.d.-b).
Anxiety Disorders	Anxiety disorders are the most common mental illness in the U.S., affecting 40 million adults in the United States age 18 and older, or 18% of the population (Anxiety and Depression Association of America, 2014).
Post-Traumatic Stress Disorder	About 6 of every 10 (or 60%) of men and 5 of every 10 (or 50%) of women experience at least one trauma in their lives. About 7 out of every 100 people (or 7% of the population) will have PTSD at some point in their lives. About 8 million adults have PTSD during a given year (U.S. Department of Veterans Affairs, 2015).
Drug Overdose Deaths	More persons died from drug overdoses in the United States in 2014 than during any previous year on record. From 2000 to 2014 nearly half a million persons in the United States have died from drug overdoses. In 2014, there were approximately one and a half times more drug overdose deaths in the United States than deaths from motor vehicle crashes (Rudd et al., 2016). By 2017 it was estimated that drug over dose deaths were 142 per day (Hedegaard et al., 2017; National Institute of Drug Abuse, 2017; President's Commission on Combating Drug Addiction and the Opioid Crisis, 2017).
Suicides	There were 41,149 suicides in 2013 in the United States (Centers for Disease Control and Prevention, 2015).

between science and fear, fear often wins.

A telling illustration may be the effort during the 1980s and early 90s, when physician Barry Marshall and pathologist, Robin Warren experienced medical establishment intimidation as they endeavored and persevered to clinically validate *Helicobacter pylori's* role in causing more than 90% of duodenal ulcers and up to 80% of gastric ulcers which were up until that time routinely classified as psychosomatic (Nobel Media AB 2014, 2005; Watts, 2005; Weintraub, 2010). Only after a 15 plus year grueling clinical research odyssey did they finally succeed (Weintraub, 2010).

Years earlier at the closing of the 60s, a parallel and significantly larger state of affair was unfolding on the national stage. Psychedelics, understandably, were rapidly coming under the microscope for their recreational misuse, which culminated in the earlier discussed placement of these substances in Schedule I of the emerging CSA in 1970. This in turn contributed to this rapidly evolving field of research being stalled in situ, well before large scale phase 3 clinical trials could be initiated, completed, data compiled and analyzed, and results peer-reviewed to deduce these substances therapeutic efficacy for the behavioral disorders in which they were being studied.

With psychedelics, along with a number of other psychoactive substances, having been organized under Schedule I of the CSA over the past approximately one-half century, with the stated premise "drugs with no currently accepted medical use" (Drug Enforcement Administration, 2017), one might argue that an unintentional scientific medical bias evolved. This may have indirectly contributed to a multi-decade long deterring of clinical research, such that only a handful of small scale clinical studies having been finalized to date. With stalled research in psychedelics over this extensive time period, the stated premise "drugs with no currently accepted medical use" may have subtly and unintentionally institutionalized itself into a scientific medical norm.

5. Operationalizing forward

Addressing the mental and behavioral health challenges in the US and globally will not be accomplished simply by new medicines. Medicines may not be the most appropriate, effective or acceptable therapies for many people. Furthermore, medicines that are not accessible or used properly in the context of supportive behavioral interventions may do little to address mental health challenges. Among medicines, psychedelic type substances may potentially prove to be most appropriate, suitable, and with an acceptable benefit to risk ratio for certain (yet to be defined) populations of people with mental illness. Going forward, the US and other nations, along with partnering research institutions and funders, need to collectively collaborate together to expand all aspects of research in this endeavor.

5.1. Research in new and emerging areas can be appropriately guided with the convening of a research summit

Given the state of this nation's mental health crisis, the Federal Government is uniquely positioned to lead a multi-day international summit on the state of the science surrounding the field of psychedelic research as part of overall psychotherapeutic treatments for mental health disorders. Convening a summit demonstrates the Federal Government's willingness to engage in paradigm shifting endeavors through the creation of a framework that can begin developing the necessary policy, regulatory, and clinical capacity prerequisites to effectually advance this research. Through this summit, leading national and international subject matter experts would be solicited to present on the full range of issues, to include but not limited to: the potential uses of these substances; their physical, psychological, and sensory effects including adverse effects and overdose; their physical and chemical properties and pharmacology; their traditional and modern cultural uses; the current state of scientific medical research (e.g. treatment resistant depression, anxiety, addiction, and PTSD); and national and international policy implications. Conducting a summit with this level of detail provides Federal Government executive level decision makers the critical information necessary to: identify phase 3 clinical research trials (e.g., type and extent of clinical trials needed to determine therapeutic efficacy for the psychedelic substances in the disorders studied); the capital resources and time required to complete these clinical trials; addressing ethical issues surrounding the use of these agents; and collectively deciding how best to update current policies and regulations to advance this research, "with the goal of ensuring that the nation's drug policies are informed by science." (National Institute on Drug Abuse, 2016).

5.2. Funding research

There should be no illusion to the challenges that lay ahead in conducting this research and by no means is this process a sprint, but instead be regarded as nothing short of a marathon. It will take committed, combined, and collegial leadership from all affected Departments and agencies actively engaged to see this endeavor through. Currently identified psychedelic agents such as DMT, psilocybin, and mescaline are naturally occurring, and agents such as LSD and MDMA have existed for decades beyond their patent expirations. Given the enormity and immediacy of the mental health crisis, the lack of financial incentives for the private sector to engage in this research, and the sheer magnitude of research needed to determine the therapeutic efficacy of these agents; it's in the Federal Government's strategic interest to fund this field of research.

6. Summary

We are facing in the US and globally a multigenerational crisis of epidemic proportions due to mental health related disorders with loss of life, profound reduction in quality of life, with increasing recognition that more needs to be done (Centers for Disease Control and Prevention, 2017; Office of Disease Prevention and Health Promotion, 2017; The Pew Charitable Trusts and John D. and Catherine T. MacArthur Foundation, 2015, 2016). Mental health disorders, including treatment resistant depression, anxiety, addiction, and PTSD, have and will continue their combined overt and covert steady-state weakening of the private and public sectors which in turn will continue to undermine our overall economic structure (National Institute on Drug Abuse, 2017; West, 2016). It is the responsibility of the Federal Government to undertake those challenges that simply are too great for the private sector to tackle itself. Nonetheless, the private sector has both a potential role and opportunity, and balanced regulatory approaches can incentivize the commitment of the private sector in co-developing profoundly needed new medicinal treatments (U.S. Food and Drug Administration, 2017c). Endeavoring to alter the trajectory of this mental health crisis through conducting research is one where the combined collaborative efforts of the Federal Government, public, and private entities will be required, with Federal Government leadership, intervention, and partnership being essential. An illustration of this is the FDA's efforts to listen to and then work to incentivize the pharmaceutical industry to develop abuse deterrent opioids to find safer ways to alleviate pain and suffering, efforts that resulted in the development and approval of more than ten such advances in pain medicines in the last few years (Schnoll and Henningfield, 2016; U.S. Food and Drug Administration, 2017c;

Table 8
USPHS Commissioned Corps Officer, CAPT Sean J. Belouin, reflective tenets for an enduring, science-centered, research-guided mental health policy.

"We must seek the truth, through science, by pursuing research."
"We must have the acknowledgment, willingness, and resolve, to engage in clinically validating potential paradigm shifting treatment endeavors, even when at times they may run counter to cultural norms, cherished ideologies, and time-honored belief systems."
"As a nation, if we can overcome fear and lead the world by putting humanity on the moon, we must overcome 50 years of legacy fear and lead in this research."

Volkow and Collins, 2017).

This commentary has focused on the scientific foundation for understanding the nature, etiology and prevalence of various mental and behavioral disorders and the clinical advances in potential treatments. However, as evident from the provisions of the CSA, science is not the only consideration in health policy. As discussed in this commentary and elsewhere in this special issue of Neuropharmacology, the CSA was developed during a time of fear, political concern, and misinformation about psychedelic substances that led to establishing substantial barriers impeding their research and potential clinical uses. Conversely, personal and social factors, along with new emerging clinical scientific information, are relevant to the resurgence of interest in research and potential application of certain psychedelic substances. Given the extent and prevalence of brain-related disorders, it seems likely that few scientists in the field have not themselves been influenced in their research interests and policy opinions based on their own professional and personal experiences involving family, close colleagues, and friends who have suffered from numerous mental health disorders. Such experiences galvanize a deep personal commitment to serve humanity through pursuing scientific research and clinical treatment development, and this is the case with the authors of this commentary. From these perspectives, we close this commentary with reference to Table 8, which summarizes three reflections of author CAPT Belouin.

Disclaimer

The views, opinions, and content of this publication are those of authors CAPT Sean J. Belouin, and Jack E. Henningfield, and do not necessarily reflect the views, opinions, or policies of the US Public Health Service, the US Department of Health and Human Services, and the Substance Abuse and Mental Health Services Administration.

Conflicts of interest

Through, Pinney Associates, JEH has consulted and/or are presently on the evaluation and regulation of pharmaceutical products including opioid and nonopioid analgesics, psilocybin, and other CNS acting products.

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