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EDITORIAL

Psychiatry might need some psychedelic therapy

In historical and modern-day studies, psychedelic drugs have shown promise in managing a variety of psychiatric disorders, but their medical use has often raised controversies. The controversies have related to social, political, and legal challenges.

History

Although anthropological evidence suggests that classic psychedelic drugs (hereafter, 'psychedelics') have been used by various indigenous peoples as sacraments and healing agents before recorded history, in the mid-twentieth century they came to occupy a place at the cutting edge of psychiatric research (Johnson, Richards, & Griffiths, 2008). Although some psychiatrists and researchers might be under the impression that this interest was a fad, this is far from the case. Over 1000 papers were published describing the treatment of over 40,000 patients with psychedelics (Grinspoon, 1981). The discovery of lysergic acid diethyamide (LSD), with its extremely powerful subjective effects caused by infinitesimal doses, and with its structural similarity to the newly-discovered neurotransmitter serotonin, was a strong contributor to the emerging neuroscientific model that took hold in the 1950s and 1960s. In large part this new biobehavioural understanding of brain function came to replace psychodynamic models as the predominant paradigm in psychiatry.

In addition to the role of psychedelics as tools for investigating the biological substrates of the mind and behaviour (considered two sides of the same coin by the present author), promising therapeutic applications were investigated, with particularly promising findings in the treatment of both addiction and cancer-related psychiatric existential distress (Johnson & Griffiths, 2017). However, despite initial excitement, research on these drugs became increasingly marginalized due to their growing use outside of clinical research settings, and their resulting association with the counter-culture movement in the late 1960s and early 1970s. These compounds are powerful tools. Like all powerful tools, use by the incautious and unwise can (and did) lead to demonstrable harms (Carbonaro et al., 2016; Johnson et al., 2008).

Although a few investigators who abandoned a scientific approach became 'poster children' for why these tools could not be trusted to scientists for human research, psychiatric pioneers such as Humphry Osmond, Abram Hoffer, Walter Pahnke, and Sidney Cohen, who are scientific heroes to the present author, were more representative of the many scientists who conducted ethical and responsible human research with psychedelics, and who knew that addressing the very real risks of these compounds was essential to making scientific and therapeutic progress. Unfortunately for investigators like these, and for patients who might have benefitted from the fruits of cautious human psychedelic research decades ago, the early promising scientific threads of psychedelic research remained dangling for decades (Tupper, Wood, Yensen, & Johnson, 2015).

Re-emergence

In the 1990s a small number of investigators in Europe and the US re-initiated human studies with psychedelics. Non-human research in the intervening decades had identified agonist activity at the 5-HT2a receptor as a key mechanism underlying the effects of psychedelics (e.g. Glennon, Titeler, & McKenney, 1984), which include LSD as well as psilocybin (present in many species of mushrooms), mescaline (present in peyote and other cacti), and dimethyltryptamine (DMT; present in a wide variety of plants). Studies by researchers in the modern era have followed established safety guidelines for administering psychedelics (Johnson et al., 2008). Like the best of the original era of research, these guidelines involve careful screening and preparation before drug administration sessions, intense monitoring during sessions, and follow-up care involving both clinically supportive discussion of session experiences and assessment for any adverse effects resulting from the session. Moreover, modern investigators have often approached this research using methods and technologies that were non-existent or not fully established in the earlier era of research, including psychometrically validated scales, double-blind and even more complex designs, and brain imaging. These early studies led to more studies at a growing number of prominent universities as the safety and potential efficacy of clinical psychedelic research was demonstrated. Therapeutic studies using psychedelics have been reported for depression and anxiety related to cancer and other life-threatening illness (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), treatment-resistant depression (Carhart-Harris et al., 2016; Palhano-Fontes et al., 2018), tobacco addiction (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Johnson, Garcia-Romeu, & Griffiths, 2017), and alcohol addiction (Bogenschutz et al., 2015).

Some studies have been randomized trials, while others have been initial open-label pilot trials designed to establish safety in new populations and test the waters for future randomized trials. Remarkably, some of these studies have reported rapid efficacy persisting for at least 6 months after one or a few administrations. In comparison, ketamine, which is under investigation for depression treatment and has greater addiction potential than psychedelics (Johnson, Griffiths, Hendricks, & Henningfield, 2018; Kolar, 2018), has been considered rightly a potential breakthrough for showing immediate antidepressant effects that persist for about a week after administration (Molero et al., 2018). Therefore, psychedelics might be considered to have even greater breakthrough potential.

Consistent with these laboratory studies, a growing number of epidemiological studies have found suggestive associations between naturalistic use of psychedelics and positive outcomes using regression models controlling for other variables including use of other drugs. For example, one study, based on a nationally representative survey of over 190,000 individuals, found that lifetime classic psychedelic use (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015), including psilocybin use (Hendricks, Johnson, & Griffiths, 2015), was associated with reduced psychological distress and suicidality in the US adult population. Potentially suggestive of anti-addiction effects, another study, based on over 25,000 individuals, suggested that psychedelic use (broadly defined) was associated with reduced recidivism from drug-related and other criminal activity among drug-involved criminal offenders undergoing community supervision (Hendricks, Clark, Johnson, Fontaine, & Cropsey, 2014).

Psychiatry needs help

Psychiatry, and society itself, finds itself faced with greater challenges than ever before. The US, home of the present author, is facing epidemic rates of suicide (Stone et al., 2018) and opioid addiction fatalities (Kolodny et al., 2015). Tobacco addiction remains a staggering killer, with about a half million people in the US (U.S. Department of Health & Human Services, 2014), and about six million people, globally, dying from tobacco related disease annually (World Health Organization, 2011). Bucking a decades-long trend in the opposite direction, between 1999 and 2013, mortality among middle-aged white, non-Hispanic adults in the US (i.e. a relatively advantaged demographic) showed a marked increase, primarily due to substance use and suicide (Case & Deaton, 2015). These are behaviourally mediated problems—the turf of psychiatry.

The last major advance in the treatment of depression was ~30 years ago with the clinical approval of the first selective serotonin reuptake inhibitors. Even these were simply more selective and safer compounds capitalizing on general mechanisms at play for older generations of antidepressants developed in the 1950s. Make no mistake, these are critical tools in the therapeutic toolbox that have helped many people. Meta-analysis suggest that effect sizes are relatively modest (e.g. Cipriani et al., 2018), but even small effect sizes for depression can be of critical help for those whose depression puts them at risk for suicide. However, there is a clear need for, and substantial room for, improvement. The state of addiction medicine is likewise disappointing. For many, but not all substances of addiction, approved medications are available that perform better than placebo. Even with these important medications, relapse rates are substantial and in dire need of improvement (McLellan, Lewis, O'Brien, & Kleber, 2000).

Aside from the need for more effective treatment options, psychiatry is in desperate need of fundamental mechanistic advances. Several years ago, the US National Institute of Mental Health (NIMH) made the decision to no longer fund research that only uses the Diagnostic and Statistical Manual of Mental Disorders (DSM) to describe psychiatric illness, due to the framework's relative lack of scientific rigour. Unlike other areas of medicine, psychiatry relies on a largely superficially descriptive, rather than mechanistic, understanding of its various disorders. Surely, this relative dearth of a mechanistic understanding of the various disorders must be related to psychiatry's slow and modest advances in treatments, and resulting unmet clinical needs.

The present author holds that psychedelics may be poised to make fundamental advances in a mechanistic (both biological and psychological) understanding of psychiatric disorders. It should be curious, and indeed, raise suspicions of 'snake oil,' that psychedelics are showing promise for supposedly distinct and wide-ranging psychiatric disorders, including depression and anxiety, and addictions across a variety of drugs. However, an emerging biological narrative might be unfolding, related to the ability of these drugs to acutely increase global brain network synchronization, and to disintegrate default mode network activity, a biological pattern of connectivity that may underlie the sense of self (Carhart-Harris et al., 2012, 2017). If continued research shows psychedelic therapy to cause lasting changes in default mode network and other brain network activity across multiple disorders, then the common biobehavioural mechanism at play may rest in the long-term adjustment of rigid, sub-optimal brain network activity associated with the narrowed behavioural and mental repertoires common to all of these disorders (Nichols, Johnson, & Nichols, 2017). Whether it is the self-persecutory thoughts and decreased activity in those with depression, the apprehensive thoughts and preventative behaviours in those with anxiety disorders, or the high rates of drug self-administration to the exclusion of other priorities (and accompanying hopeless thoughts) with substance use disorders, these might all be

conceptualized as addiction, broadly defined. Other commonalities, for example, potential inflammation effects common across some psychiatric disorders which might be addressed by potential long-term anti-inflammatory effects of psychedelics, discussed by Flanagan and Nichols in this issue, might also emerge. Therefore, not only might psychedelics provide robust efficacy across multiple disorders, they might also constitute breakthrough tools in taking psychiatry to the next level in terms of understanding mechanistic commonalities across supposedly distinct disorders.

Importantly, the mechanisms underlying psychedelic efficacy might be both biological *and* psychological. For decades, non-empirically-grounded terms such 'ego death' have been used to describe the acute effects of these drugs. As discussed above, research now suggests a very real, empirically supported biology may underlie such effects. Moreover, patients in research trials commonly report narrative, psychological content at play when psychedelic therapy appears successful, such as achieving a fundamental, molar understanding of themselves, their connections to others, and insights into the issues from which they suffer (e.g. Noorani, Garcia-Romeu, Swift, Griffiths, & Johnson, 2018). Indeed, it seems that, unlike with most psychiatric medications, patients are doing their own psychological 'heavy lifting' when they receive psychedelic therapy, perhaps affording a greater sense of agency compared to other psychiatric medications. In this respect, the return of psychedelics to psychiatry might constitute a return of psychiatry to its roots, before the focus on biology and the brain took center stage, with a psychological understanding focused on the sense of self as it interfaces with personal history and the environment, as in the psychodynamic models which once predominated. However, this homecoming now involves a more empirically grounded approach bridging both psychology and neuroscience—the best of both worlds.

Whatchu talkin' 'bout, Willis? These are drugs of abuse!

An understandable initial reaction by many psychiatrists and researchers may be skepticism. Especially for those on the clinical front lines, the implicit association with psychedelics is negative. As they are controlled substances, their use is often associated with the use of other illicit substances. Also their use, particularly in uncontrolled contexts, can lead to anxiety reactions and resultant dangerous behaviour. For those with psychotic disorders or predisposed to these disorders, psychedelic use may lead to prolonged adverse reactions and harm to mental health. However, a critical distinction is that, while these factors lead to psychedelics being considered drugs of abuse or misuse when used in an uncontrolled setting, it is well established that psychedelics are not drugs of addiction or compulsive drug seeking. Moreover, modern safety guidelines squarely address these concerns to minimize such risks in clinical research, affording a radically different safety profile compared to uncontrolled psychedelic use (Carbonaro et al., 2016; Johnson et al., 2008, 2018).

If it seems strange that a class of abused drugs is being developed for therapeutic potential, consider that psychedelics are actually the only major class of abused drugs that do *not* already have therapeutic uses recognized by regulatory bodies such as the US Food and Drug Administration (FDA). While medicine is currently trying find a balance between their use and risks, opioids are indispensable to medicine as analgesics, despite being associated with high addiction potential and acute fatal overdose. Methamphetamine, amphetamine, and similar stimulants with very high addiction potential are approved for the treatment of attention deficit disorder. Cocaine is approved for topical use as an anaesthetic in otolaryngologic procedures. Benzodiazepines, barbiturates, and mechanistically related GABAergic sedatives are often abused but approved as anxiolytics and hypnotics. Finally, despite the controversy and current mixed state-federal legal status of plant cannabis in the US, there is no controversy whatsoever about the clinical use of dronabinol (tetrahydrocannabinol or THC), which was FDA approved over 30 years ago, and is used to treat chemotherapy-related nausea and vomiting, as well as appetite and weight loss in HIV patients (Because clinical development is occurring for synthetic psilocybin, rather than psilocybin-containing mushrooms, the appropriate analogy would indeed be to dronabinol rather than plant cannabis.). Drawing from these trends, it would almost be surprising if psychedelics did *not* have therapeutic potential, at least in limited circumstances, especially given their substantially lower physical toxicity and addiction potential in comparison to the other psychoactive drugs with approved therapeutic use (Johnson et al., 2018).

Why now?

Despite two decades of dormancy (mid-1970s to mid-1990s), and two decades in which professional acceptance for the few scientists involved was questionable, and the prospect of governmental funding of therapeutic studies seemed a pipe dream (mid 1990s–recently), mainstream scientific and societal acceptance of human psychedelic research seems it might be finally taking off. Perhaps the best current example is the recent publication of acclaimed author Michael Pollan's book *How to Change Your Mind: What the New Science of Psychedelics Teaches Us About Consciousness, Dying, Addiction, Depression, and Transcendence* (Pollan, 2018), currently on the *New York Times* Best Seller list. Pollan, best known for his non-fiction books on food and

agriculture, spent years delving into scientific laboratories around the world in order to render the modern era of psychedelic research digestible to Jane and John Q. Public. Whether his synthesis substantially moves the needle regarding scientific and public support for psychedelic research remains to be seen, but book sales and his high-profile interviews promoting the book would suggest it has at least piqued some substantial curiosity.

Why did it take decades for such research to reinitiate and gain hold? There were surely many factors at play at different levels of analysis, but perhaps at the molar behavioural level, time simply had to move forward, consistent with Thomas Kuhn's description of the unfolding of scientific revolutions or new paradigms (Kuhn, 1962). Kuhn cites physicist Max Planck, founder of quantum theory, in making the point: '[A] new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it' (Planck, 1949, p. 33–34).

Kuhn (1962) reminds us that Isaac Newton's *Principia* (Newton, 1687), one of the greatest scientific works in history, was not met with general acceptance for more than 50 years after its publication. Kuhn also cites Charles Darwin, whose wisdom allowed him to accurately predict a similar fate for *On the Origin of Species*, also among humanity's greatest scientific works. As Darwin (1859) wrote in the conclusion of that hallowed scientific volume:

> Although I am fully convinced of the truth of the views given in this volume under the form of an abstract, I by no means expect to convince experienced naturalists whose minds are stocked with a multitude of facts all viewed, during a long course of years, from a point of view directly opposite to mine … A few naturalists, endowed with much flexibility of mind, and who have already begun to doubt the immutability of species, may be influenced by this volume; but I look with confidence to the future, to young and rising naturalists, who will be able to view both sides of the question with impartiality (p. 481–482).

When it took generations to pass for the seminal works of Isaac Newton and Charles Darwin to take hold in humanity's collective scientific understanding, psychedelic researchers find themselves in some respectable company, to say the least. So, although those advancing the scientific and therapeutic potential of psychedelics might understandably feel frustrated at the opportunities lost, perhaps this history was to be expected.

Current issue and new directions in psychedelic research

The current issue of *International Review of Psychiatry* contains a number of exciting manuscripts focused on the scientific potential and clinical use of psychedelics, written by leading experts with backgrounds in psychiatry, psychology, neuroscience, and pharmacology. Although the focus is on the classic 5-HT2a agonist psychedelics, related compounds with differing but somewhat overlapping mechanisms, such as methylenedioxymethamphetamine (MDMA), are occasionally addressed. As clinical research interest in psychedelics is rapidly increasing, special attention has been paid to curate both summaries of the current landscape of clinical psychedelic research, as well as previously unexplored topics, including both psychological and biological mechanisms, and novel potential future therapeutic modalities and theoretical frameworks for understanding psychedelic therapy.

Psychologists Albert Garcia-Romeu, PhD, and William Richards, PhD, provide an overall view of the clinical field of psychedelic research, with a summary of past and present models for conducting therapy with psychedelics, as well as considerations for future interventions. These authors draw from recent specialization in the use of psychedelics in the treatment of addiction from Dr Garcia-Romeu, as well as from several decades of clinical experience from Dr Richards (see Richards, 2015), who is considered a living legend among psychedelic researchers, and who is perhaps the only clinical researcher whose experimental research spans both the earlier era and current eras of human psychedelic research.

Stephen Ross, MD, is an addiction psychiatrist who also has expertise in the treatment of cancer-related existential distress. Dr Ross and colleagues conducted one of the recent, large randomized, double-blind, clinical trials showing substantial and sustained anti-depressant and anxiolytic effects of psilocybin in cancer patients. Dr Ross provides a broad review of the literature on existential distress associated with cancer. He then reviews research from both the previous and modern eras of research, showing promising effects of psychedelics for this indication.

Peter Hendricks, PhD, is a clinical psychologist who is currently conducting a randomized, double-blind study examining the therapeutic potential of psilocybin in the treatment of cocaine addiction, a trial for which he recently presented promising preliminary results for psilocybin-occasioned cocaine abstinence at the 2018 meeting of the *College on Problems of Drug Dependence*. In his manuscript in this issue, Dr Hendricks provides a fascinating psychological theory of psychedelic therapy, embedding psychedelic-occasioned mystical-type experiences within the literature surrounding the psychological construct of awe. Awe refers to an experience in which a stimulus is encountered that is so vast that it prompts a modification in the sense of self, resulting in a 'small self' with therapeutic import.

Zach Walsh, PhD, a clinical psychologist in Canada with expertise in applying 'third wave' behaviour therapies to addressing intimate relationship conflict and

substance use disorders, along with Michelle Thiessen, provide a review which explores the possibility of applying third wave behaviour therapies to enhance psychedelic therapy. Third wave behavioural therapies go beyond Cognitive Behaviour Therapy (the 'second wave') to include a number of relevant constructs, such as mindfulness, to provide a sophisticated understanding of behaviour change. Such therapies include empirically supported approaches such as Dialectical Behaviour Therapy, Acceptance and Commitment Therapy, and Mindfulness Based Cognitive Therapy. After identifying implicit commonalities between third wave behavioural approaches and psychedelic therapy, these authors go on to make recommendations for the explicit integration of third wave approaches to enhance psychedelic therapy in the treatment of psychiatric disorders.

Frederick Barrett, PhD, Katrin Preller, PhD, and Mendel Kaelen, PhD, an international team of neuroscientists and psychologists with expertise in affective neuroscience and music, provide a review of the history and recent research showing the critical role of music in psychedelic therapy sessions. Moreover, they explore psychological and biological mechanisms by which psychedelics may be used as tools to understand the mechanisms for the perception of music and the mechanisms underlying profound emotional experiences in general. Even if some readers cannot follow all of the nuanced notes of their exploration, those readers are sure to be able to follow the music of this fascinating review.

Finally, pharmacologists Thomas Flanagan, PhD, and Charles Nichols, PhD, provide a review of psychedelics as anti-inflammatory agents. After reviewing the role of the 5-HT2a receptor in anti-inflammatory response, Dr Flanagan and Dr Nichols review exciting evidence from Dr Nichol's pharmacology laboratory showing that 5-HT2a receptor activation causes potent anti-inflammatory effects in non-human models at very low, sub-behavioural doses, and discuss the potential of psychedelics as a new medication class to treat inflammatory disorders. Further, they discuss the potential that such anti-inflammatory effects might in fact play a role in the persisting therapeutic effects of psychedelics for psychiatric disorders.

This issue of *International Review of Psychiatry* provides both an informative introduction to the uninitiated, as well as a more thorough exploration of psychedelic research for those who have followed this field for years, and perhaps decades! The reader is requested to explore the empirical support for the research described herein. Further, it is hoped that this issue will serve to invite both the skeptical and the enthusiastic (and ideally, those who are both) to conduct their own empirical research in this rapidly growing field. Welcome to the renaissance in psychedelic research!

Disclosure statement

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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Invited review

The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act

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ABSTRACT

This review assesses the abuse potential of medically-administered psilocybin, following the structure of the 8 factors of the US Controlled Substances Act (CSA). Research suggests the potential safety and efficacy of psilocybin in treating cancer-related psychiatric distress and substance use disorders, setting the occasion for this review. A more extensive assessment of abuse potential according to an 8-factor analysis would eventually be required to guide appropriate schedule placement.

Psilocybin, like other 5-HT2A agonist classic psychedelics, has limited reinforcing effects, supporting marginal, transient non-human self-administration. Nonetheless, mushrooms with variable psilocybin content are used illicitly, with a few lifetime use occasions being normative among users. Potential harms include dangerous behavior in unprepared, unsupervised users, and exacerbation of mental illness in those with or predisposed to psychotic disorders. However, scope of use and associated harms are low compared to prototypical abused drugs, and the medical model addresses these concerns with dose control, patient screening, preparation and follow-up, and session supervision in a medical facility.

Conclusions: (1) psilocybin has an abuse potential appropriate for CSA scheduling if approved as medicine; (2) psilocybin can provide therapeutic benefits that may support the development of an approvable New Drug Application (NDA) but further studies are required which this review describes; (3) adverse effects of medical psilocybin are manageable when administered according to risk management approaches; and (4) although further study is required, this review suggests that placement in Schedule IV may be appropriate if a psilocybin-containing medicine is approved.

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Contents

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1. Introduction

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is under development for the treatment of depression and anxiety for patients with life-threatening cancer diagnoses (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Although at a more preliminary research state, promising open label results have also been reported for treatment-resistant major depression (Carhart-Harris et al., 2016a; Rucker et al., 2017) and addiction to tobacco (Johnson et al., 2014) and alcohol (Bogenschutz et al., 2015). Such treatments would be in the form of a clinically tested drug product that would provide psilocybin doses demonstrated to be safe and effective in a formulation that assures precision in dosing, which is rarely the case for illicitly consumed mushrooms (Bigwood and Beug, 1982), and in a clinical framework that would minimize the possibility of misuse or diversion. These drug formulation and intervention parameters would be addressed in an agreed upon risk management plan and would also likely be addressed in a legally binding Risk Evaluation and Mitigation Strategies (REMS) plan (U.S. Food and Drug Administration, 2015). The REMS would be based on the studies and approaches used to ensure safe and effective use and could include: a) limitations on the dose and the number of doses that could be administered to a given patient, b) administration of the drug in clinic settings with psychological support of specially trained staff, c) a variety of restrictions on distribution, access and storage, and d) a post-marketing surveillance plan to provide the FDA with timely and comprehensive communication of unintended consequences (Blanchette et al., 2015; Brandenburg et al., 2017; Dart, 2009; Dasgupta and Schnoll, 2009; U.S. Food and Drug Administration, 2015; Wu and Juhaeri, 2016).

The benefits of psilocybin in the treatment of depression, anxiety and other disorders were first suggested in the 1960s when psilocybin was marketed in many countries, including the United States (US) under the trade name Indocybin® by the Swiss pharmaceutical company, Sandoz. Indocybin® provided a shorter acting alternative to lysergic acid diethylamide (LSD) which has a similar primary pharmacological mechanism of action, now known to be agonist or partial agonist effects at the 5-HT2A receptor (Nichols, 2016). While Indocybin® was used safely as an adjunct to psychotherapy, eventually the societal backlash in the US and other countries in the 1960s (Matsushima et al., 2009) led to a ban on marketing and possession of "hallucinogenic" drugs in the US in 1965, and led Sandoz to discontinue manufacturing and marketing of Indocybin® in 1966 (Belouin and Henningfield, 2018; Bonson, 2018; Novak, 1997). The 1970 placement of psilocybin, LSD, and other "hallucinogens" in Schedule I of the CSA did not reflect an absence of therapeutic benefit, although the scientific evidence at the time was mixed. This mixed evidence included strong (at least for the time) pharmacological studies, as discussed later in this review, along with clinical studies suggesting potential safety and efficacy that were nonetheless considered by leading researchers during the 1960s to be limited and not sufficient to support efficacy and safety claims for LSD or other hallucinogens. This situation is discussed by Bonson (2018) in her review of human LSD research and regulation, and would appear to generally apply to psilocybin, which was being administered by some of the same research programs that administered LSD. These limitations in the evidence base and the rising tide of sensational media accounts of adverse consequences of classic psychedelic use, discussed later, fueled the perception by many public and political leaders that psilocybin posed serious risks to patients and the public that did not outweigh its benefits (Belouin and Henningfield, 2018; Hofmann, 1980; Nutt et al., 2013). Therefore, having not been formally approved by the FDA for therapeutic use, psilocybin was placed in Schedule I of the CSA in 1970 and remains in Schedule I.[1]

As discussed in section 1.1, removal from Schedule I can only occur if a medicinal product containing a Schedule I substance is approved for therapeutic use as a drug by the FDA. Then, whether it will be scheduled, and, if so, into what schedule it will be placed, will be subject to the FDA's abuse potential assessment that will include an analysis of the 8 factors of the CSA (Drug Enforcement Administration, 2017a; U.S. Food and Drug Administration, 2017a). As discussed by Calderon, Hunt and Klein in this journal

[1] Schedule I of the CSA is reserved for substances determined by DEA to "have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision." This includes substances that were determined to warrant placement in Schedule I when the CSA was enacted into law in 1970, and substances that have not been approved by the FDA for medical use but were placed in Schedule I based on DEA's 8-factor analysis, or temporarily placed (also commonly termed "emergency scheduled") in Schedule I if DEA determines such placement "is necessary to avoid an imminent hazard to the public safety." For such scheduling the DEA is required to consider only factors 4, 5 and 6 of the CSA, namely, the substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health, respectively (Calderon et al., 2017; Drug Enforcement Administration, 2017a; Henningfield et al., 2017; Pinney Associates, 2016; U.S. Food and Drug Administration, 2017a).

issue, schedule placement is a process that considers "potential for abuse, medical use, and physical or psychological dependence liability," among other lines of evidence (Calderon et al., 2017). For example, approval of the Schedule I compounds dextrorphan and difenoxin (with atropine) resulted in dextrophan becoming unscheduled, and difenoxin (with atropine) being placed into either Schedule IV or V, depending on dose. Similarly, the previously Schedule I compound piperazine was descheduled. Approval of an oral form of dronabinol (marinol) was initially placed in Schedule II and, in 1999, rescheduled to Schedule III, leaving cannabis and forms of dronabinol that were not approved drug products in Schedule I. As noted by Calderon et al., approved drugs with hallucinogenic effect vary widely in the scheduling from the Schedule I status of most hallucinogenic drugs without approved medical use, to Schedule II phencyclidine, Schedule III ketamine, and Schedule IV lorcaserin, and the not scheduled 2,5-dimethoxy-4-iodoamphatamine, also known as DOI (Calderon et al., 2017).

Thus, if an NDA for a psilocybin product is submitted to the FDA and approved, then the CSA would require its rescheduling, and schedule placement would be determined by evaluation of its overall abuse potential (Drug Enforcement Administration, 2017a; Henningfield et al., 2017; U.S. Food and Drug Administration, 2017a). In fact, as discussed in Belouin and Henningfield (2018) (in this journal issue), there is increasing evidence supporting the eventual development and submission of an NDA for a psilocybin-containing product. Emerging science suggesting benefits of a psilocybin product warrant an official breakthrough designation by the FDA to address the large number of cancer sufferers whose depression and anxiety are not responsive to conventional therapies (Belouin and Henningfield, 2018; Griffiths and Johnson, 2015; Ross et al., 2016). In addition, advances in risk management and monitoring, which were absent in the earlier heyday of psychedelic research, necessitate that we revisit the potential for approving a classic psychedelic (i.e., psilocybin) as a medicine because risk management, particularly in the legally binding approach of REMS, is intended to provide conditions for distribution, use, oversite and other factors to ensure safe use (McCormick et al., 2009; U.S. Food and Drug Administration, 2015).

Clinically, chemically, and pharmacologically, psilocybin has similarities with several substances that were generally termed "hallucinogens" in the 1950s and have been termed "psychedelics" since the 1960s. Although both of these terms are sometimes used to refer to compounds with other primary mechanisms of action (e.g., ketamine; salvinorin A, methylenedioxymethamphetamine or MDMA), 5-HT2A receptor agonist compounds, including psilocybin, LSD, mescaline, and dimethyltryptamine (DMT), are specifically referred to as "classic psychedelics" or "classic hallucinogens." Although there are similarities in the effects, patterns of use and past clinical applications of LSD, psilocybin, and other classic psychedelics, the present evaluation is focused on a drug product in which the active ingredient is psilocybin. Moreover, approval would include not only the compound, but also its labeling and restrictions on manufacturing, marketing and use. These additional domains are critical to the benefit to risk evaluations which are foundational for drug evaluation and approval (U.S. Food and Drug Administration, 2017c).

Research and licit clinical use of LSD and psilocybin greatly slowed in the 1960s as amendments in 1962 and 1965 to the 1938 US Food Drug and Cosmetic Act imposed severe restrictions on distribution, possession, use, and research (Barrigar, 1964; Bonson, 2018; Grabowski, 1976; Grinspoon and Bakalar, 1979). As discussed elsewhere in this journal issue and in other publications (Nutt, 2015; Nutt et al., 2013; Scientific American Editors, 2014; Sinha, 2001; Spillane, 2004; Woodworth, 2011), legal restrictions have greatly constrained research; however, research did not altogether cease, and began to accelerate by the late 1980s in preclinical laboratories, and in clinical settings by the late 1990s. This resurgence has been fueled in part by renewed appreciation of the potential importance of these substances in advancing the science of the brain and behavior and for their potential significance in the treatment of disease. Moreover, since the 1970s extensive national drug use and effects surveillance systems have been developed in the US, which show that the prevalence of abuse and serious adverse events associated with psilocybin and other classic psychedelics are relatively low compared to other major classes of abused drugs (Johnson, Hendricks, Barrett, Griffiths, submitted). In addition to the more recent clinical research, the reassuring results from these epidemiological data also increase interest in the evaluation of psilocybin as a potential therapeutic medicine (Roseman et al., 2017; Rucker et al., 2017). Because the FDA approved therapeutic medicines cannot be listed in Schedule I of the CSA, consideration of changes in scheduling recommendations becomes an important part of the clinical development of psilocybin. As discussed in this review the evidence continues to support the conclusion that if a psilocybin drug product was approved by the FDA, CSA scheduling would remain appropriate. Considerable additional study will be required for the development of an FDA-acceptable NDA, including the abuse potential assessment section of the NDA according to the FDA's abuse potential assessment guidance (U.S. Food and Drug Administration, 2017a). Thus, it is premature to come to a definitive conclusion about which schedule would be most appropriate. This review is intended to stimulate further research and thinking in this area through its evaluation of key abuse potential-related science presently available and considered through the approach of the CSA 8-factor analysis which is the key approach of the CSA for developing scheduling recommendations. The review includes a preliminary scheduling conclusion based on the research considered and the opinions of these authors, along with key gaps in the research that will also likely be of importance to the FDA.

1.1. Abuse potential and drug scheduling in the context of the CSA

The scheduling process for new drugs officially commences upon approval of the product by the Controlled Substances Staff (CSS) of the FDA, who provide an 8-factor analysis based, in part, on the sponsor's submission of an NDA that includes the sponsor's abuse potential assessment that has been prepared according to the recommendations in the FDA's guidance for sponsors: Assessment of the Abuse Potential of Drugs (U.S. Food and Drug Administration, 2017a). The FDA obtains review and input from the National Institute on Drug Abuse (NIDA). Then, the Assistant Secretary of the US Department of Health and Human Services transmits her/his recommendation to the Drug Enforcement Administration (DEA) within the Department of Justice (DOJ). Since the spring of 2016, the schedule recommendation by the Department of Health and Human Services must be accepted and finalized by the DOJ/DEA within 90 days unless there is a compelling basis for placement in a different schedule (U.S. Congress, 2015). Finalization of the scheduling action will follow the standard federal rulemaking process (U.S. Food and Drug Administration, 2015; U.S. Office of the Federal Register, 2011).

The scientific assessment of the abuse potential (also commonly referred to as "abuse liability" and "addiction potential") is based on the scientific evaluation of substances going back to the early twentieth century search for less abusable analgesics (Jasinski et al., 1984). By the 1960s such evaluations included stimulants, sedatives, and psychedelics. This science and its methods of assessment, along with other considerations including population level public health impact, were brought together in the 1970 CSA in the form of

8 specific factors for the assessment of what was then termed "abuse potential." That term recognized that problematic use of substances could occur in people who were not physiologically dependent or addicted, and by drugs (e.g., cocaine, cannabis, LSD and psilocybin) for which it was unclear (at the time) if they posed a physiological dependence risk.

Analysis of all 8 factors is required to guide the FDA and DEA recommendations for CSA scheduling of approved medicines (Drug Enforcement Administration, 2017a; U.S. Food and Drug Administration, 2017a). Consistent with the observations that abuse potential varies widely across substances, approved medicines can vary from control in Schedule II to Schedule V (i.e., C-II to C-V), in which C-II is for those of greatest concern (e.g., cocaine, morphine, and phencyclidine), C-V is for those of sufficient concern to warrant control but for which abuse potential appears lowest among controlled substances (e.g., low dose codeine in combination with acetaminophen, lacosamide, and pregabalin). Of intermediate concern for control is Schedule IV, which includes diazepam, mazindol and tramadol, and Schedule III, which includes dronabinol, ketamine, and nalorphine.

1.1.1. FDA is the sponsors' focal point for the NDA including its abuse potential assessment

The FDA is the focal point for abuse potential assessment, and works with the sponsor to determine the range of studies needed to enable its review of the NDA in order to determine approvability, the scheduling recommendation, and all aspects of labeling (some of which are based on the abuse potential assessment and scheduling). The NDA's abuse potential assessment submission required by the FDA is comprised of 5 modules that include the sponsor's scheduling proposal and rationale in Module 1, and a summary and thorough discussion of all abuse related nonclinical and clinical data in Module 2. Modules 3, 4 and 5 include complete study protocols and data addressing chemistry, in vitro and nonhuman pharmacology, and clinical studies including the integrated summary of safety (ISS), respectively. The sponsor need not submit an 8-factor analysis but sponsors often include one in their module 1 rationale.

The present 8-factor analysis benefits from the fact that psilocybin is not a new chemical entity devoid of real world (i.e., "community") data. Rather we have been able to draw from more than a half century of research and various types of therapeutic use, as well surveillance epidemiology. However, it suffers from the fact that most of the research has not been conducted as part of a cohesive sponsored drug development program that had FDA input throughout much of development. Thus, in this review we attempt to note particular strengths and weaknesses in studies and gaps in the study portfolio that will likely need to be addressed before filing an NDA.

2. Evaluation of the abuse potential of psilocybin according to the 8 factors of the CSA

The following 8-factor evaluation of psilocybin may be considered a substantially abbreviated effort compared to the 100-200 page Module 1 and Module 2 abuse potential assessment submitted as part of a potential NDA, though substantially more detailed than the summary 8-factor analysis that might be prepared by the FDA and published by DEA in the US Federal Register in support of their scheduling recommendations (Drug Enforcement Administration, 2002; 2013, 2014, 2017b).

2.1. Factor 1: Actual or relative potential for abuse

Although the 1970 placement of psilocybin in Schedule I impeded research, more than a half century of research, clinical experience, and surveillance provide a substantial basis for evaluating the abuse potential of psilocybin according to Factor 1 and the seven additional factors. This experience has shown that psilocybin does have a potential for abuse, with preclinical and clinical studies providing information about this potential for abuse relative to other substances, scheduled and nonscheduled.

2.1.1. Preclinical studies

Psilocybin has been evaluated in a variety of preclinical models of physical dependence and abuse potential, yielding qualitatively generally similar findings with LSD. These similarities included increased pulse, respiratory rate, and pupil diameter but no physical dependence or withdrawal (Martin, 1973). Preclinical models of abuse potential suggest weak reinforcing effects and weak stimulus generalization to substances of high abuse potential (Baker, 2017; de Veen et al., 2017; Fantegrossi et al., 2008). For example, Fantegrossi, Woods and Winger (Fantegrossi et al., 2004) evaluated the classic psychedelic compounds N,N-dimethyltryptamine (DMT), mescaline, and psilocybin in rhesus monkeys with histories of self-administering 3,4-methylenedioxymethamphetamine (MDMA), a compound which is not a classic psychedelic but which produces some overlapping subjective effects in humans (Studerus et al., 2010). As shown in Fig. 1, none of the classic psychedelics generated reliable self-administration, though during occasional sessions, animals self-administered all available doses and appeared intoxicated post-session. The study authors concluded "… the present data provide further evidence that several classic psychedelic drugs from two distinct structural classes do not reliably maintain contingent responding in rhesus monkeys." This pattern of sporadic self-administration may indicate that these compounds have weak reinforcing effects, or, alternatively, mixed reinforcing and aversive effects."

The apparent weak reinforcing effects of psilocybin and other classic psychedelics may account for why there have been relatively few nonhuman studies examining reinforcement models. In contrast, many more nonhuman research studies with classic psychedelics have used drug discrimination models. Discriminative stimulus effects refer to the ability of a drug, upon administration, to serve as a cue that can predict environmental contingencies, e.g., which of two levers will result in the delivery of a reward if pressed. Discriminative stimulus effects can therefore be thought of as the ability of the drug to be recognizable to the organism (and therefore serve as a cue). Discriminative stimulus effects are different from reinforcing effects, and have different biological bases (Johnson and Ettinger, 2000). Discriminative stimulus effects may be relevant to drug reinforcement when a test drug reliably substitutes in discrimination testing for a drug with well-established reinforcing effects, e.g., when a drug reliably substitutes for amphetamine. In such cases it is likely (although not certain) that the test drug will also be shown to be reinforcing when directly tested with self-administration procedures. Discrimination studies have strongly contributed to our understanding of psilocybin and other classic psychedelics. For example, Harris and Balster compared psilocybin to amphetamine in a rodent model for assessing behavioral and discriminative effects (Harris and Balster, 1971). They found that psilocybin served as a discriminative stimulus but that these stimulus-control effects were weak compared to amphetamine. Schechter and Rosecrans (1972) employed a T-maze discrimination procedure and found psilocybin and mescaline, but not amphetamine, reliably substituted for LSD in rats trained to discriminate LSD from saline. Similarly, another study found the psilocybin failed to substitute for amphetamine in rats trained to discriminate amphetamine from saline (Kuhn et al., 1974). In another study rats trained with psilocybin generalized fully to psilocin (the active

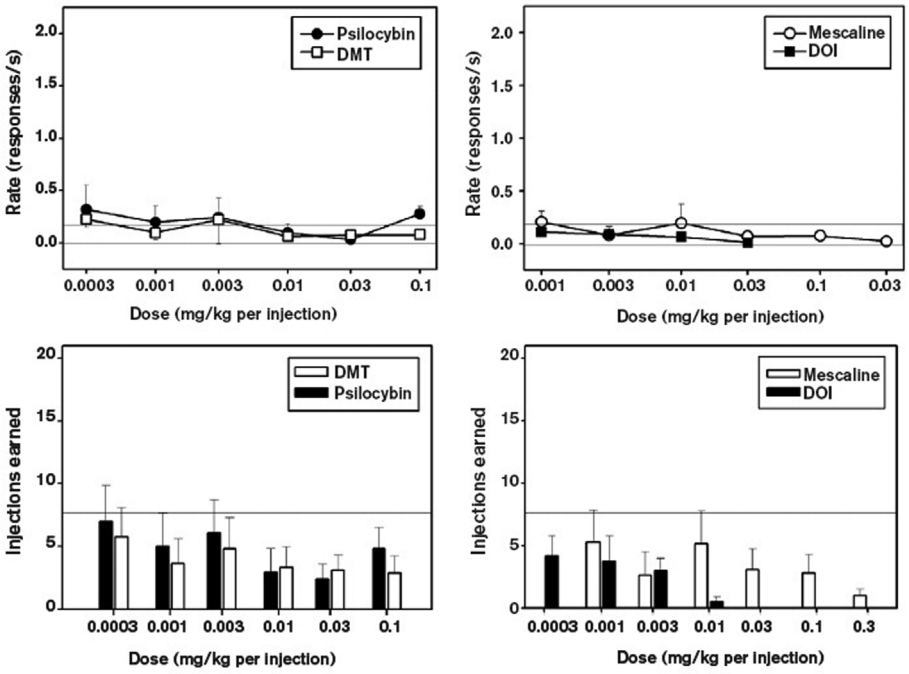

Fig. 1. The two upper panels show mean response rates (±SEM) during self-administration of classic psychedelic compounds by rhesus monkeys making lever presses under an FR-30 schedule of reinforcement. Left panel shows psilocybin and DMT; right panel shows mescaline and 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI). The two bottom panels show the corresponding mean number of injections earned (±SEM) during these self-administration sessions. For all panels, the light horizontal lines show the range for saline response rates (upper panels) and saline injections earned (bottom panels; with the bottom of the range at 0). For all panels, n = 4. Figure from Fantegrossi et al. (2004), Fig. 1.

metabolite of psilocybin) and to LSD but not to mescaline, which is considered a classic psychedelic of the phenethylamine-based structural class rather than the tryptamine-based structural class of which psilocybin is a member (Cunningham and Appel, 1987; Koerner and Appel, 1982). Another study, however, found that psilocybin fully substituted for mescaline in rats trained to discriminate mescaline from saline (Appel and Callahan, 1989). A study in pigeons found psilocybin to fully substitute for LSD in LSD trained subjects (Jarbe, 1980).

Winter et al. (2007) evaluated psilocybin and other classic psychedelics following treatment with several antagonists for specific serotonin receptor subtypes. They concluded: "the present data indicate that the stimulus properties of psilocybin in the rat are broadly compatible with those of other ergoline, indoleamine, and phenethylamine classic psychedelics. However, significant differences are apparent as well" and "psilocybin induces a compound stimulus in which activity at the 5-HT2A receptor plays a prominent but incomplete role" and "the full generalization of psilocybin to LSD and to DOM is completely blocked by the selective 5-HT2A receptor antagonist, M100907, but stimulus control by psilocybin is only partially antagonized by M100907" (Halberstadt and Geyer, 2011; Winter et al., 2007).

These studies confirm that psilocybin produces discriminative effects that do not generalize to amphetamine, and psilocybin does not substitute in amphetamine trained animals. Moreover, psilocybin discriminative effects are likely mediated by psilocin, the active metabolite produced *in vivo* by dephosphorylation of psilocybin (Passie et al., 2002). In addition, findings demonstrate that psilocybin produces weak and transient reinforcing effects that are consistent with community level observations (also see Factor 4) suggesting that the vast majority of people who have used psilocybin do not develop compulsive patterns of use. Instead, more typically individuals report only a few uses of psilocybin, consistent with a substance of low overall abuse potential. The findings also suggest a need for additional studies to better understand the mechanisms of action of psilocybin and other psychedelic substances and how these may contribute to their apparent low overall abuse potential (Baker, 2017; Hayes and Greenshaw, 2011).

2.1.2. Human abuse potential assessment

Psilocybin has not been examined in an abuse potential study that would meet the criteria recommended by the FDA in its 2017 Guidance: Assessment of the Abuse Potential of Drugs; however, many clinical laboratory studies have been conducted since the mid-1950s in which key measures of abuse potential have been assessed. This work began at the US Public Health Service Addiction Research Center (ARC) of the National Institute of Mental Health, during the time that the methods of human abuse potential were being developed. Studies with psilocybin and LSD contributed to the development of abuse potential assessment methods, in part because it was quickly recognized that they differed in several key respects from opioids, sedatives, and stimulants which were then emerging as prototypic substances of abuse. In contrast to these drugs, any abuse potential-related effects associated with LSD, psilocybin, and related substances appeared to be unreliable and limited to specific conditions such as time of assessment, dose, and individual, social and experiential factors. In further contrast, the predominant and most reliable effects seemed to be effects thought to limit use and abuse (e.g., fear, anxiety, dysphoria, and physical discomfort including gastrointestinal upset). Thus, a leading addiction scientist and director of the ARC, Dr. William Martin, stated the following in a 1973 review of preclinical studies of psychedelic drugs: "The abuse of LSD-like hallucinogens came as somewhat of a surprise to many of the early experimenters with these drugs" (Martin, 1973, p. 149). Nonetheless, while he did acknowledge that certain doses of LSD could produce pleasure in some volunteers (Belleville et al., 1956), Martin's (1973) review indicated that most of the preclinical and clinical findings of the

1950s and 1960s were not indicative of a prototypic drug of abuse.

Psilocybin studies at the ARC commenced a few years following studies of LSD, with the first human reports published in 1959 by Isbell (1959a; b). The initial studies occurred early in the development of human abuse potential assessment research when human volunteers with histories of substance abuse were evaluated for potential euphoriant effects, which were considered predictive of abuse potential (Isbell, 1956). These studies contributed to the development of human abuse potential assessment as measures evolved to characterize not only the euphoriant effects that characterized opioids and stimulants, but also the dysphoric effects that distinguished classic psychedelics such as LSD and psilocybin. At the same time theories of addiction and addiction liability assessment were evolving from the focus on physical dependence and withdrawal that had dominated the prior few decades of opioid-focused studies to a greater focus on the acute subjective and behavioral effects of drugs that contributed to their self-administration and abuse, regardless of whether physical dependence and withdrawal were evident (Isbell, 1956; Wikler, 1961).

During the 1950s and 1960s, the ARC demonstrated that among the strongest predictors of abuse potential was the reliable and dose-related production of euphoriant effects as measured by self-reported, and observer-evaluated effects including liking of the drug, apparent pleasure, confidence, and sense of well-being (Isbell, 1956). These findings led to development of systematic approaches to the assessment of drug liking, drug type identification, and frequent physiological correlates including pupil diameter and withdrawal symptoms (Fraser et al., 1961; Jasinski and Henningfield, 1989; Jasinski et al., 1984). The methods developed have continued to be refined over the past half century and remain the foundation for human abuse potential assessment studies (Carter and Griffiths, 2009; Griffiths et al., 2003; U.S. Food and Drug Administration, 2017a).

In the early 1960s, an important addition to the study of human abuse potential was the development of the ARC Inventory (ARCI), a participant-completed questionnaire. Studies of LSD and psilocybin contributed to the development of this questionnaire and a broader understanding of abuse (Haertzen and Hickey, 1987; Haertzen et al., 1963; Hill et al., 1963). Table 1 provides more background on the ARCI and its importance in characterizing the abuse potential of LSD and psilocybin. The full ARCI contained more than 500 items, however, 49 items or fewer were found to provide valid and reliable characterization of abuse-related qualitative effects of several categories of drugs with various subscales emerging from studies of drug administration in human volunteers. The most prominent predictor of abuse potential was the Morphine Benzedrine Group (MBG) scale that came to be accepted as an important measure of euphoria. In contrast, a scale that was derived from LSD studies, the LSD scale, came to be known as the dysphoria and psychotomimetic scale, which captured fear and anxiety and seemed to predict low abuse potential. LSD and psilocybin most reliably elevated scores on the LSD scale, but frequently also, at a certain dose and in some individuals, elevated scores on the MBG scale, but generally at a lesser magnitude than opioids and stimulants (Haertzen and Hickey, 1987; Jasinski and Henningfield, 1989; Jasinski et al., 1984).

A seminal study that was that published by Isbell in 1959 found that psilocybin produced qualitatively similar effects to LSD with spontaneously reported onset of subjective effects at about 10–15 min following oral ingestion (Isbell, 1959a). In contrast to the initial euphoric effects that characterized opioids, stimulants, sedatives, and cannabis, Isbell found that the initial effects of psilocybin were more likely to include anxiety along with altered sensations. These effects were often followed within the next 15 min by increasingly strong anxiety and fear, visual distortions and difficulty thinking, though some subjects experienced elation and expressed “continuous gales of laughter” (p. 32). He concluded that LSD was approximately 100–150 times as potent as psilocybin on subjective effects and physiologic measures including increased pupil diameter, heart and respiratory rate, and reduced threshold of the patellar reflex, with similar time course of onset but shorter duration of effects by psilocybin compared to LSD. Additional ARC studies are described in factor 2 as they pertain to understanding the mechanisms of action of psilocybin.

2.1.3. Clinical trials relevant to abuse potential assessment since 2000

Since 2000 there have been several clinical trials that have included measures related to the assessment of abuse potential. For example, one study (Griffiths et al., 2011) showed that all four oral doses of psilocybin examined (~0.071, ~0.143, ~0.286, and ~0.429 mg/kg) produced statistically significant increases over placebo for both the A (amphetamine) scale and LSD scales of the ARCI. The MGB scale did not significantly differ between placebo and psilocybin at any dose. Another study (Bogenschutz et al., 2015) included a short form of the ARCI. Unfortunately, the open label study was neither placebo controlled, nor did it include a positive control for comparison. Such conditions are especially important for drugs that produced mixed and weak signs of abuse potential. Nonetheless, their findings were typical of those previously observed for psilocybin and LSD. The authors observed weak elevations of both the MBG and LSD scales following oral administration of 0.3 and 0.4 mg/kg psilocybin, in volunteers with histories of alcohol dependence. Whereas these effects do not indicate substantial abuse potential, they cannot be used to rule out significant potential for abuse because in the absence of comparators, the weak MBG effect might be related to the population and other design aspects of the study. This study, like others discussed in Factor 6 (Griffiths et al., 2016; Ross et al., 2016) also documented reports of acute elevations in fear and anxiety in some patients that are predictive of low abuse potential as well as a subsequently emerging sense of contentment that is not associated with a strong motivation to use repeatedly and chronically. It is also important to note that these recent studies have gone to further lengths to maximize the pleasantness of the physical environment and establish interpersonal rapport between participants and staff (Johnson et al., 2008) compared to the older ARC studies. Therefore, MBG scores in these recent studies might overestimate the drug euphoria that would be experienced in a less than optimal environment. As in Factor 6, the mixed acute subjective effects of psilocybin included fear, anxiety, pleasure, happiness and contentment, and thus are consistent with those of the early 1960s from the ARC, however, these studies were not designed as human abuse potential studies and the putative abuse potential related effects must be interpreted cautiously. In particular, the participants in the recent cancer trials (Griffiths et al., 2016; Ross et al., 2016) were patients with severe anxiety and or depression whose therapeutic improvements in mood were long-lasting and not necessarily reflective of abuse potential.

2.2. Factor 2: Scientific evidence of its pharmacological effect

It has been estimated that there were more than one thousand scientific and clinical studies of classic psychedelics including LSD and psilocybin published through the 1960s (Drug Enforcement Administration, 1995; Grinspoon, 1981; Grinspoon and Bakalar, 1979; Johnson and Griffiths, 2017), and several thousand more published since the 1960s (Sellers et al., 2017).

Initial conclusions drawn by ARC researchers have been replicated by others as discussed in various reviews (Johnson et al., 2008; Nichols et al., 2017). In brief, in addition to physiological

Table 1
The Addiction Research Center Inventory.

Through the 1950s the term for assessing potential addictive and abuse-related drug effects was "addiction liability" assessment and the major focus of assessment was on the development of tolerance and the emergence of withdrawal signs and symptoms upon discontinuation of drug administration (Himmelsbach and Andrews, 1943). In the late 1950s Isbell, Frazier and colleagues at the ARC came to conclude that the mood and behavior altering effects of drugs contributed to and were predictive of the risk of abuse and addiction and that these could be evaluated by psychometric instruments. The simplest and most commonly relied upon measure in human abuse potential studies to support NDAs to the FDA is the drug liking scale that was originally a five-point scale in which subjects rated their liking of the drug from 0 (not at all) to 4 (an awful lot). This scale development benefitted from the then recent observations of Beecher (Beecher, 1952, 1957) who demonstrated that such scales could be used to reliably assess pain and analgesia (Beecher, 1952, 1957; Lasagna et al., 1955). Such positive mood alterations could be produced by drugs of abuse that were not then known to produce physical dependence and withdrawal, and by single doses of opioids in former opioid users (referred to as "post-addicts") who were no longer physically dependent (Jasinski, 1977; Jasinski and Henningfield, 1989; Jasinski et al., 1984; U.S. Food and Drug Administration, 2017a).
As predominant theories of addiction at the time included the potential importance of personality disorders, a psychologist who was expert in the Minnesota Multiphasic Personality Inventory and testing, Charles Haertzen, was hired in 1959, to take the lead in developing a comprehensive instrument to better characterize and differentiate the several categories of substances that were abused as well as the personality characteristics of those who used them. The resulting Addiction Research Center Inventory (ARCI) contained more than 500 true and false items, but shorter versions containing 40 or 49 items were most commonly used in human abuse potential studies. The ARCI scale that provided the most robust indicator of high abuse potential was the Morphine Benzedrine Group (MBG) scale, commonly referred to as the "euphoria" scale because it was empirically derived based on the response of volunteers to the prototypic euphoriants morphine and Benzedrine® (hence, the MBG scale) which produced robustly elevated mood and feeling states. In contrast, a scale based on responses to LSD (LSD scale) was distinguished by a cluster of items, that included unpleasant, dysphoric, or psychotomimetic responses to LSD (hence the LSD scale) that were associated with a lower propensity to compulsively or frequently self-administer the substance; it was often referred to as the "dysphoria" scale (Hill et al., 1963; Jasinski et al., 1984). It also included scales based on clusters of items that were associated with amphetamine administration (the A scale) and one that reflected the somewhat overlapping and sedating effects of pentobarbital, chlorpromazine, and atropine group of drugs (the PCAG scale). Most drugs of high abuse potential produced elevations in the scores on the MBG scale as well as on the specific scale that reflected their pharmacological class. Thus, alcohol, barbiturates, opioids, and stimulants could all increase MBG scale robustly as well as the scale that was specific to their class. Chlorpromazine and atropine, by contrast, which were rarely abused, did not reliably elevate MBG scale scores but might elevate LSD scale scores. LSD elevated LSD scale scores and sometimes elevated MBG scale scores and liking scores, reflecting their overall low abuse potential and diverse effects that can range from fear and anxiety to pleasure, depending much on dose, time since drug, experience, and other factors (Griffiths et al., 2008).
Examples of a few of the items that distinguished drugs likely to elevate scores on the MBG scale as compared to items characterizing the LSD scale are the following: "I would be happy all the time if I felt as I do now" - scored positively on the MBG scale and negatively on the LSD scale; "I am in the mood to talk about the feeling I have" and "I feel more clear-headed than dreamy" - were both score positively on the MBG scale and were not included on the LSD scale. The LSD scale also contained numerous items reflective of mixed mood effects, e.g., "I feel anxious and upset" and "I have a weird feeling" – both scored positively; negatively scored items included "I feel very patient", and "My movements are free, relaxed and pleasurable"; and, items reflective of introspection and negative feelings included "I have a negative disturbance in my stomach", "Some parts of my body are tingling", and "It seems I'm spending longer than I should on each of these questions" (Haertzen and Hickey, 1987; Jasinski and Henningfield, 1989).
Over more than 50 years of research, it became clear that drugs with the highest overall abuse potential were those that produced robust increases in scores on drug liking scale and the MBG scale, and low effects on the LSD scale (Griffiths et al., 2018; Griffiths and Balster, 1979; Haertzen and Hickey, 1987; Jasinski and Henningfield, 1989; Jasinski et al., 1984). Liking scales have since evolved into the more commonly used 100-point (or 100 mm) visual line analog scales and the ARCI often replaced with scales to assess positive (pleasant) and negative (unpleasant) effects as described in early 2000 expert reviews and advised by the FDA in its abuse potential assessment guidance (Carter and Griffiths, 2009; Griffiths et al., 2003; U.S. Food and Drug Administration, 2017a).
The ARCI helped elucidate a major difference in nature and magnitude of the abuse potential that is associated with psychedelics, as compared to substances that carry a high risk of compulsive patterns of repetitive use and abuse including amphetamine, cocaine, the cigarette form of nicotine delivery, prototypic opioids, and sedatives, as compared to substances with substantially lower potential for compulsive use and abuse, such as LSD and psilocybin (see also Table 1).

and behavioral effects discussed in Factor 1, it was demonstrated that repeated dosing produces diminished effects (tolerance) and that cross-tolerance occurs between psilocybin and LSD (Abramson et al., 1960; Isbell et al., 1961), but not to tetrahydrocannabinol (THC) indicating different mechanisms of action (Isbell and Jasinski, 1969). Effects of psilocybin are qualitatively similar to those produced by mescaline, however, mescaline is less potent but longer acting (Wolbach et al., 1962). The effects of psilocin are the same as those by psilocybin except that it is more potent and shorter acting than psilocybin (Isbell et al., 1961). It is now understood that psilocybin is a pro-drug, converted by dephosphorylation to the pharmacologically active psilocin (Nichols et al., 2017; Passie et al., 2002). Strong early support for this contention was provided by data showing that although psilocin is slightly more potent than psilocybin, the ratio difference in potency between the two compounds (in both humans and nonhumans) is nearly identical to the ratio of their respective molecular weights (i.e., they are equipotent on a molecular basis) (Koerner and Appel, 1982; Wolbach et al., 1962). Isbell and Logan (1957) demonstrated that chlorpromazine administration reduced and could partially reverse the effects of LSD. Nonetheless, the pharmacology and mechanisms of action of psilocybin and LSD are similar in many respects, although psilocybin is shorter acting and at least 100 times less potent than LSD (Isbell, 1959a; Sellers et al., 2017). Research has also shown the 5-HT2A antagonist ketanserin to block most of the effects of psilocybin (Kometer et al., 2012, 2013; Quednow et al., 2012; Vollenweider et al., 1998), although ketanserin does not block certain psilocybin effects including the slowing of binocular rivalry, reductions in arousal/vigilance (Carter et al., 2007), and attentional impairment (Carter et al., 2005).

More than 100 species of mushrooms, in the genus *Psilocybe*, contain psilocybin (Johnson and Griffiths, 2017; Stamets, 1996). Its agonist activity at the 5-hydroxytryptamine (HT)2A receptor appears to account partially for its behavioral effects, however, the mechanisms of action of its full range of effects have not been fully elucidated (Nichols, 2016; Winter et al., 2007). Psilocybin is a substituted indolealkylamine and with diverse serotonergically mediated effects and little affinity for dopamine D2 receptors (Halberstadt and Geyer, 2011; Passie et al., 2002). It is among the structural class of classic psychedelics based on the tryptamine structure, including an indole ring (Passie et al., 2002). Albert Hofmann, the discoverer of LSD and chemist at the Swiss Sandoz Pharmaceutical Company, isolated psilocybin from Central American mushrooms (*Psilocybe mexicana*) in 1957, and synthesized the substance in 1958 (Passie et al., 2002). Its binding to and agonist effects at 5-HT2A serotonin receptors are associated with dilation of the pupils (mydriasis), reduced threshold for knee reflex, and commonly increased heartrate and blood pressure, and feelings of nausea (Isbell, 1959a; b). Its effects on mood and feeling can include visual and auditory hallucinations, distortion of visual and auditory stimuli, altered temporal sense, and alteration of body image. Its effects have the potential to mimic psychotic states which contributed to its designation, along with LSD, as a psychotomimetic. The effects that contribute to introspection and often increased receptivity to advice and psychotherapy contributed to its use in psychotherapy, as well as to investigations by

psychologists and psychiatrists in efforts to better understand the moods and states of their patients (Hofmann, 1980; Matsushima et al., 2009; Passie et al., 2002).

Studies of LSD began in the 1940s with many of the same laboratories, including Sandoz, investigating the generally similar-acting psilocybin in the 1950s and 1960s. However, as discussed above in Factor 1, caution must be made in generalizing findings, including mechanisms of action, from LSD to psilocybin and vice versa. The resurgence of research beginning slowly in the 1970s and accelerating in particular since the 1990s has been rapidly increasing the understanding of the effects and mechanisms of action of psilocybin, including its general safety and the conditions of safe use (Griffiths et al., 2008; Nichols et al., 2017).

2.2.1. Tolerance and physical dependence

Tolerance refers to decreased response with repeated administration of a drug. Tolerance to the psychological and physiological effects of psilocybin is strong. Moreover, there is cross-tolerance between psilocybin and LSD. However, physical dependence and withdrawal, which refer to adverse effects upon discontinuing repeated use of a drug, have not been documented (Abramson et al., 1956; Abramson and Rolo, 1965; Balestrieri, 1967; Isbell, 1959a; Isbell et al., 1961; Passie et al., 2002; Wolbach et al., 1962). It is plausible that the FDA would recommend that sponsors collect a more rigorous evaluation of physical dependence and withdrawal in animals consistent with its 2017 abuse potential guidance, perhaps as part of a safety evaluation of high dosages. However, it is also plausible that the FDA might not require such additional studies given that there is little evidence that psilocybin produces physical dependence and withdrawal, and the treatment protocols under investigation would not involve repeated daily dosing.

2.2.2. Toxicity

Unlike prototypic opioids and sedatives of abuse, psilocybin carries a low risk of overdose toxicity by respiratory depression or cardiovascular events or other causes of death associated with substances of abuse. The LD50 of intravenous psilocybin has been determined to be above 250 mg/kg (with 200 mg/kg killing no animals, and 250 mg/kg killing a small portion of animals (Cerletti, 1958). Its lethal dose in humans has been theoretically estimated at approximately 1000 times an effective dose (Gable, 2004), which is an amount that is likely not possible for an individual to consume when in the form of psilocybin-containing mushrooms. The authors are aware of only one documented case of acute overdose poisoning death likely caused by psilocybin (Lim et al., 2012). Specifically, a 24-year old female, who had received a heart transplant 10 years prior due to end-stage rheumatic heart disease, experienced cardiac arrest 2–3 hr after consuming psilocybin-containing mushrooms, and subsequently died. Toxicology revealed only psilocin (active metabolite of psilocybin) and THC. Thus, the only known acute fatal overdose from psilocybin appears to be in a medically compromised individual. Given psilocybin's moderate pressor effects, individuals with such serious cardiac vulnerability would be excluded from recently approved psilocybin trials and should be excluded from any potential non-research future approved clinical use.

One study examined isolated nonhuman animal organs and found no significant effect in the rat uterus or the guinea pig duodenum or seminal vesicle (Cerletti, 1958). Administering relatively large doses to waking nonhuman animals of a variety of species led to acute autonomic effects including mydriasis, piloerection, hyperglycemia, hypertonia, and pulse and breathing irregularities (Cerletti, 1958), with similar effects later observed in Rhesus macaques (Horibe, 1974; Passie et al., 2002). A micronucleus study in mice found no evidence that psilocybin administration resulted in chromosome breaking (Van Went, 1978).

Hollister reported that human administration of psilocybin resulted in decreased urinary excretion of inorganic phosphorus and reduced circulating eosinophil levels, as well as pupillary dilation and increased deep tendon reflexes (Hollister, 1961). In addition, Hollister (1961) reported on a single participant who was administered psilocybin on a daily basis for 22 days, with doses ranging from 1.5 to 27 mg per day. Before and during that course of administration, no chronic changes were observed for any metric assessed: total leukocyte count, absolute eosinophil count, hemoglobin, curea nitrogen, creatinine, glucose, serum proteins, cholinesterage activity, serum glutamic-oxaloacetic transaminase titer, cholesterol and EEG tracing. Gouzoulis-Mayfrank et al. (1999) found that human psilocybin administration resulted in no change in cortisol, prolactin, or growth hormone. Johnson et al. (2012) found that in a within-subject, double-blind, placebo-controlled study, oral psilocybin (0, ~0.071, ~0.143, ~0.286, and ~0.429 mg/kg) caused headaches which were dose-dependent in terms of incidence, duration, and severity. Headaches had delayed onset relative to subjective drug effects, were transient, and ceased within 24 hr of psilocybin administration. Although mechanisms response for these delayed onset headaches are not known, one possible mechanism is nitric oxide release.

2.2.3. Pharmacodynamics

The acute effects of psilocybin have been studied in animals and humans over a broad range of doses over several decades (Isbell et al., 1961; Johnson et al., 2008; Nichols et al., 2017; Wolbach et al., 1962). Like other classic psychedelics, the acute psychological effects following psilocybin administration are varied and often intense, although strongly dose-dependent and dependent on the interpersonal and physical environment (Griffiths et al., 2011; Hasler et al., 2004; Johnson et al., 2008). These psychological effects often include perceptual changes that are primarily visual but can also include synesthesia across sense modalities, emotional changes in which both positive and negative emotions can be far more intense than normal, cognitive changes that can include alterations in time perception, and an introspective focus on personal history, life relationships and circumstances, and changes in sense of self (Johnson et al., 2008). In a retrospective analysis of 409 psilocybin administrations to 261 healthy participants by a single research group, a few interpersonal factors among many were found to influence psilocybin response (Studerus et al., 2012). Specifically, high trait absorption scores, being in an emotionally excitable and active state before administration, and having fewer recent psychological problems all predicted pleasant and mystical-type effects, while high trait emotional excitability, younger age, and a PET imaging setting, all predicted unpleasant or anxious effects (note that pleasant and unpleasant effects within the same session are not mutually exclusive).

The early studies by Isbell and colleagues documented the time courses of onset of autonomic and psychological effects, generally beginning within 30 min of oral ingestion, peaking within 1–2 h, and subsiding over the next few hours, with a duration of action shorter than those produced by LSD and mescaline (Wolbach et al., 1962). Since 2000, several studies have been conducted in which the pharmacodynamics have been evaluated over multiple measures and doses. Hasler et al. investigated the acute psychological and physiological effects of oral psilocybin in a double-blind, placebo-controlled study in healthy volunteers at dose of 0, 0.045, 0.115, 0.215, and 0.315 mg/kg administered in a cross-over design at intervals of at least two weeks (Hasler et al., 2004). Measures included cardiovascular variables, plasma concentrations of a several hormones, and several measures of mood, subjective response and behavioral performance. Blood samples were

collected pre-dosing and at 105 and 300 min post-administration. Blood pressure was measured 30 min pre-dosing and at 5, 30, 60, 90, 120, 165, and 210 min post-administration. Electrocardiograms (EKG) were continuously monitored for 24 hr. The main findings were orderly dose- and time-dependent effects that were significantly altered at many measures and timepoints. Subjective effects began to onset about 20–40 min post-administration, peaking at about 60–90 min and diminishing over the next 60–90 min. One subject became markedly anxious at the 0.315 mg/kg dose and his anxiety gradually subsided to complete resolution within 6 hr after drug administration. No significant changes were observed in EKG or body temperature, but prolactin, thyroid-stimulating hormone, adrenocorticotropic hormone, and cortisol were increased by at least the 0.315 mg/kg dose. Another dose effect study of psilocybin ranging into higher doses examined 0, ~0.071, ~0.143, ~0.286, and ~0.429 mg/kg using a placebo-controlled, double-blind, crossover design (Griffiths et al., 2011). Sessions were 1 month apart, and a 14-month follow-up was conducted. Acute psychological effects largely replicated those shown in the earlier study, with time course data showing orderly dose- and time-related effects. In addition, this study found that 39% of participants reported extreme anxiety/fear for at least one of the two highest doses. End of session data showed psilocybin caused significant dose-related increases in mystical experience using the Mystical Experience Questionnaire. Moreover, a month after sessions, the experiences associated with the two highest doses were rated as having substantial personal and spiritual significance. Participants attributed improvements in attitudes, mood, and behavior to the two highest doses. At the 14-month follow-up, such ratings were largely unchanged from ratings made a month after each session. Improvements in attitudes, mood, and behavior were also observed in dose-blinded community members who had regular contact with participants.

More recently, two clinical trials discussed below in Factor 6 (Griffiths et al., 2016; Ross et al., 2016) also documented the time course of several physiological, mood and behavioral variables. However, persisting for far longer than these acute effects were the therapeutic effects. Specifically, both studies showed that psilocybin caused significantly and clinically significant reductions in symptoms of depression and anxiety lasting at last 6 months after psilocybin administration. Griffiths et al. studied patients with clinical anxiety and depression related to their life-threatening cancer diagnoses (Griffiths et al., 2016). Informed by data from previous psilocybin dose effects studies (Griffiths et al., 2011; Hasler et al., 2004) they compared a moderately high dose (~0.314 or ~0.429 mg/kg) to a dose sufficiently low that it was expected to be devoid of therapeutic effects (~0.014 or ~0.043 mg/kg), using a randomized, double-blind, cross-over counterbalanced design. The two doses were administered 5 weeks apart, and participants returned for 6-month follow-up. Measures of mood, attitudes, and behaviors were self-reported by participants and rated by staff and community observers throughout the study. On drug administration days, research staff were present with the patients continually during the approximately 7–8 hr long experimental session that included a battery of physiological, subjective and behavioral measures 10 min before capsule administration, repeated 30, 60, 90, 120, 180, 340, 300, and 360 min after oral capsule administration. As shown in Fig. 2, there were significant dose and time-related effects on most measures including non-clinically severe increases in heart rate and blood pressure, and observer-rated anxiety, nausea, joy/intense happiness, peace/harmony, psychological discomfort and physical discomfort, but no serious adverse events attributed to psilocybin. Ross et al. (2016) used a largely similar design with a moderately high dose of psilocybin (0.3 mg/kg) being administered in one session, and a comparison compound administered in another session, with the exception that the comparison compound was niacin rather than a very low dose of psilocybin. Largely similar acute effects were reported, and no serious adverse effects were attributed to psilocybin.

2.3. Factor 3: Current scientific knowledge regarding drug

Psilocybin is a phosphate derivative of N,N-dimethyltryptamine that is typically is observed in concentrations ranging from 0.1 to 1.5% at least ten species of the *Psilocybe* genus of mushrooms, and in some species of other genera (Stamets, 1996). Virtually all illicit use is in the form of mushrooms, including dried and fresh mushrooms. They are often eaten whole, with or without food, but can also be heated in water to produce an active aqueous extraction (a “tea”), or powdered and consumed in capsules (if dried) (Stamets, 1996). Cultivated psilocybin-containing mushrooms have been shown to vary in psilocybin content by a factor of 4, while “street samples” of psilocybin-containing mushrooms have been shown to vary in psilocybin content by an astonishing factor of 10 (Bigwood and Beug, 1982). These wild variations in psilocybin content, combined with the variations in methods for consumption described above, suggest that dosing is not well controlled in typical illicit use. This contrasts with approved studies that administer known doses of psilocybin. There have been occasional reports of intravenous injection psilocybin in research (Carhart-Harris et al., 2016b; Petri et al., 2014; Schartner et al., 2017; Waugh, 2016) although we are aware of no reports of illicit use of psilocybin by injection.

There has been considerable progress elucidating the effects and mechanisms of action of psilocybin in animal and human studies. It is well-established that psilocybin, like other classic psychedelics, has agonist or partial agonist activity at 5-HT2A receptors (Nichols, 2016). Carbon 14-label psilocybin studies revealed that approximately 50% of orally ingested psilocybin is absorbed and rapidly systemically distributed. The isotope is distributed almost uniformly throughout the whole body. Studies of metabolites by Holzman and Hasler (Hasler, 1997; Holzmann, 1995) reported by Passie et al. (2002), found four metabolites: d 4-hydroxy-N,N-dimethyltrypt-amine (Psilocin); d 4-hydroxyindole-3-yl-acetaldehyde (4H1A); d 4-hydroxyindole-3-yl-acetic-acid (41-IIAA); and d 4-hydroxytryptophol (41-IT), with a first hepatic bypass effect leading to extensive conversion to psilocin within 30 min. This corresponds to the beginning of physiological and psychological effects in the time course described below. Passie et al. (2002) reported that psilocin levels peak at about 50 min post oral administration and then slowly decline over the next 5 hr, again roughly corresponding to physiological and psychological effects, for a half-life estimated at 163 ± 64 min orally (Passie et al., 2002; Sellers et al., 2017).

Considerable progress has been made in recent years to understand the mechanisms of psilocybin's therapeutic effects. Resting state function magnetic resonance imaging shows that psilocybin administration acutely alters brain network activity. This includes decreased connectivity within the default mode network, which is a system of brain regions that supports internal focus (Carhart-Harris et al., 2012; Johnson and Griffiths, 2017). However, there is no well-documented theory about how such acute effects, lasting only hours, lead to therapeutic benefits lasting months and possibly a year or more. It has been suggested that the acute destabilization of brain networks by psilocybin (which may stem from receptor level effects via amplification of neuronal avalanches) may provide the opportunity to alter brain network activity in a persisting fashion (Johnson and Griffiths, 2017; Nichols et al., 2017). Such a mechanism has been suggested as consistent with the evident importance of the appropriate context and importance of psychotherapy in the therapeutic benefits of both

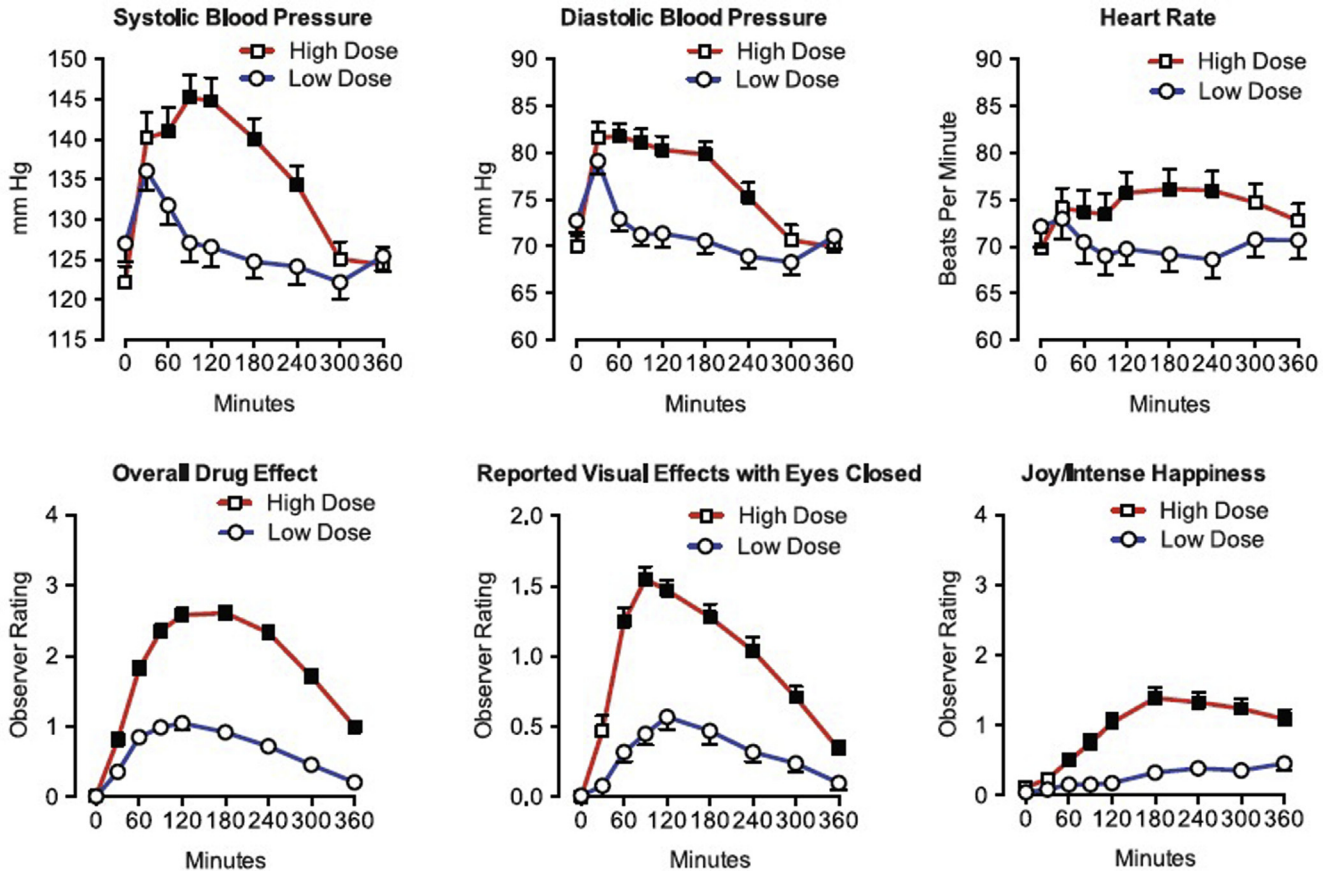

Fig. 2. Cardiovascular and observer-rated effects of oral psilocybin in cancer patients (n = 50). Each panel shows the mean (±SEM) within-subject time-course effect of a moderately-high (~0.314 or ~0.429 mg/kg) versus low, placebo-like (~0.014 or ~0.043 mg/kg) dose of psilocybin. For observer ratings, the Y-axis spans the range of possible scores. Filled squares indicate that planned comparisons showed the high dose condition significantly differed from the low dose condition at that time-point ($p < 0.05$). Figure from Griffiths et al. (2016), Fig. 2).

psilocybin and LSD (Hofmann, 1980; Johnson et al., 2008; Johnson and Griffiths, 2017). That is, the acute effects of psilocybin in altering brain network dynamics may set the occasion for such networks to re-establish themselves in altered ways after the conclusion of acute effects; the overall context and the non-drug therapeutic aspects of the intervention may play a role in shaping such re-established networks.

As reviewed by Nichols et al. (2017), it is now known that serotonergic-acting psychedelics, including psilocybin, have anti-inflammatory effects and may have efficacy in treating some inflammatory diseases. They observed that inflammation of the brain "has been linked to several psychiatric disorders including depression, addiction, and neurodegenerative disorders such as Parkinson's and Alzheimer's disease." Insofar as elevated serotonin levels are associated with inflammation it is plausible that psilocybin has anti-inflammatory effects in the brain, possibly involving serotonergic systems that contribute to its therapeutic effects (Nichols et al., 2017).

2.4. Factor 4: History and current pattern of abuse

Table 2 provides a summary overview of psilocybin and psilocybin-containing mushrooms in cultures dating back at least 7 millennia. From the perspective of understanding the abuse potential of psilocybin it is important to note that the history of psilocybin use has primarily involved naturally occurring psilocybin containing mushrooms. Use of these mushrooms by non-indigenous individuals in the US and elsewhere began soon after Wasson's discovery of mushroom ceremonies in the late 1950s (Stevens, 1987). An exception was the brief distribution of a pure psilocybin containing drug product branded as Indocybin® as an adjuvant to psychotherapy or a tools in experimental psychiatry, free of charge for a few years in the early 1960s by the Swiss Sandoz pharmaceutical company (Lee and Shlain, 1992; Passie et al., 2002). In those days this general approach was permitted for drugs that were not approved for therapeutic use (Bonson, 2018). Nonetheless, research on psychedelic substances began to slow in 1962/1963 when US scientists were required to seek federal approval for evaluations of psilocybin or LSD (Stevens, 1987).

2.4.1. United States national surveys

Various national agencies monitor a broad range of substance use related behaviors, effects, concomitants and treatment seeking. Together, these characterize the prevalence and trends and effects related to various substances geographically and demographically. A brief summary of the major surveillance systems follows.

2.4.1.1. Treatment episode Datasets (TEDS). TEDS is an annual record of U.S. substance abuse treatment admissions. The methods of the survey and data collection are described elsewhere (Substance Abuse and Mental Health Services Administration, 2017a). An estimate of treatment for psilocybin use disorder specifically cannot be assessed because it has not emerged as a sufficiently large cause of substance use disorders to warrant its own category, thus, the

Table 2
History of psilocybin use and in culture.

7000 BCE-5000 BCE – Mushroom cave paintings from Tassilli, modern-day Algeria (Samorini, 1992)
4000 BCE – Possible evidence of psilocybin-containing mushroom use in cave paintings in modern-day Spain (Akers et al., 2011)
4000 BCE-900 CE – Mushroom stones and other artifacts from cultures throughout the Americas, including Mayan (de Borhegyi, 1961; Lowy, 1971; Schultes, 1969; Schultes et al., 2001; Truttman, 2012)
1600 – Spanish colonizers documented religious mushroom use by indigenous people in Mexico, considered it devil worship, and persecuted its use. Sacramental use was driven underground for the next 400 years (Schultes, 1969; Schultes et al., 2001).
1957 – Spanish conqueror accounts of mushroom use had come to be considered myth (Schultes, 1969). Then, following earlier suggestive evidence by R. Schultes (Schultes, 1939, 1940), R.G. Wasson became the first non-indigenous individual to participate in and document sacramental psilocybin-containing mushroom use by indigenous people (Mazatec society in Mexico) since European colonization (Wasson, 1959; Wasson and Wasson, 1957)
1958–1959 – A. Hofmann, using mushrooms provided by R.G. Wasson, isolated psilocybin and psilocin, then developed synthesis of each (Hofmann, 1958; Hofmann et al., 1958; Hofmann et al., 1959)
1959 – Clinical research was begun; initial research did not appreciate the powerful influences of set and setting, resulting in erratic outcomes (Delay et al., 1959)
1960s – Societal, legal, and political backlash emerged against the psychoactive drug excesses of the 1960s, along with the associated "counter-culture", the promotion of psychedelics as a panacea for achieving personal enlightenment and a utopian transformation of society, as opposed to use primarily as potential medicines in people with illness
Early 1960s – Indocybin marketing for research by Sandoz requiring therapeutic interventions, ending in 1966
1970 – US Controlled Substances Act listed psilocybin in Schedule I, along with LSD, heroin and other substances of serious societal and public health concern, thus prohibiting therapeutic use, and imposing extensive barriers to possession and research
1971–1990s – Human psilocybin research was largely dormant until the late 1990s when a few laboratories in Europe renewed interest (Spitzer et al., 1996; Vollenweider et al., 1997). Human psilocybin research then began in the U.S. at the University of New Mexico (Bogenschutz et al., 2015; Strassman, 2001) [initiated but unpublished psilocybin results], Johns Hopkins University (Griffiths et al., 2018), the University of Arizona (Moreno et al., 2006), the University of California, Los Angeles (Grob et al., 2011), and New York University (Ross et al., 2016).

TEDS assesses a composite category termed "hallucinogens," which includes LSD, DMT, "STP" (2,5-dimethoxy-4-methylamphetamine or DOM), mescaline, peyote, psilocybin, and other (unnamed) "hallucinogens". Common substances sometimes considered to be "hallucinogens" but which are included in other TEDS categories (rather than the "hallucinogen" category) are MDMA and phencyclidine (PCP). As shown in Table 3, for all years from 2005 to 2015, "hallucinogens" were consistently reported as the primary substance of abuse in 0.1% of all admissions aged 12 + years. In 2015 those who reported "hallucinogens" as their primary substance of abuse at admission were 74.9% male and – on average – 28 years of age, and 43.6% had not used "hallucinogens" in the past month (only 25.9% had used daily in the past month). To provide some perspective we include TEDS data for opiates, cocaine and alcohol. Together these data show that among substances of abuse, treatment seeking for the entire category of "hallucinogens" constitutes a very small fraction of reports to TEDS with no evidence of increasing trends over the last decade of reports.

2.4.1.2. Drug Abuse Warning Network (DAWN). The DAWN, which monitored U.S. drug-related visits to emergency departments, was discontinued after 2011. The methods and its scope of data collection are described elsewhere (Substance Abuse and Mental Health Services Administration, 2013). As shown in Table 4, from 2004 to 2011, the data suggest an increasing trend in psilocybin-related emergency department (ED) visits. However, the signal is so small, compared to "pain relievers," cocaine, and alcohol that an increase from 0.2 to 0.4 of all ED visits must be interpreted with caution. In terms of rates, psilocybin-related ED visits increased from 1.0 per 100,000 population in 2004 to 1.9 per 100,000 population in 2011.

2.4.1.3. National Survey on Drug Use and Health (NSDUH). The NSDUH is an annual survey of substance use and mental health issues in US civilians ≥ age 12. Methods for some NSDUH items changed in 2015, necessitating trend breaks in some cases. However, items related to "hallucinogens" were not modified. As shown in Table 5, between 2009 and 2015, lifetime use of psilocybin was consistently reported by about 8.5% of NSDUH respondents aged 12 and older, with a low of 8.1% (in both 2011 and 2012) and a high of 8.7% (in 2013). The reported lifetime use rate in 2015 was 8.5%. The methods of the survey, including specific questions are described in detail elsewhere (Substance Abuse and Mental Health Services Administration, 2017b).

2.4.1.4. Monitoring the future (MTF). The MTF is a survey of substance use and attitudes of U.S. secondary school students, college students, and young adults. It does not ask its participants about prevalence of psilocybin use; however, the survey does ask about "hallucinogens", which is broken down into LSD and

Table 3
Treatment episode datasets (TEDS): Rate of various drugs as the primary substance of abuse among persons 12 years and older, 2005–2015.

Primary Substance	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total	1,896,299	1,962,664	1,969,862	2,074,974	2,055,914	1,932,524	1,936,278	1,834,591	1,762,015	1,639,125	1,537,025
Hallucinogens											
n	2045	1644	1651	1917	1880	1791	1998	2155	2177	1899	1917
%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Opiates											
n	332,401	353,899	364,614	411,301	439,826	443,405	486,729	488,038	507,989	501,680	526,686
%	17.5%	18.0%	18.5%	19.8%	21.4%	22.9%	25.1%	26.6%	28.8%	30.6%	34.3%
Cocaine											
n	268,402	277,852	259,973	239,342	193,419	158,780	152,349	126,371	106,594	88,623	74,710
%	14.2%	14.2%	13.2%	11.5%	9.4%	8.2%	7.9%	6.9%	6.0%	5.4%	4.9%
Alcohol[a]											
n	746,544	781,349	804,581	860,742	856,180	782,764	759,017	709,891	654,808	591,404	521,089
%	39.4%	39.8%	40.8%	41.5%	41.6%	40.5%	39.2%	38.7%	37.2%	36.1%	33.9%

[a] Alcohol only or with a secondary drug.
Source: (Substance Abuse and Mental Health Services Administration, 2017a)

Table 4
Drug abuse warning network (DAWN): Total ED visits (any type) for various drugs, 2004–2011.

Drugs	2004	2005	2006	2007	2008	2009	2010	2011
Total ED visits	2,537,722	3,009,025	3,441,855	3,998,228	4,383,494	4,595,261	4,916,328	5,067,374
Psilocybin								
number of ED visits	2947	2937	3557	4006	5422	4087	4539	6048
% of all ED visits	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Rate per 100,000 population	1.0	1.0	1.2	1.3	1.8	1.3	1.5	1.9
Opiates/opioids								
number of ED visits	299,498	388,873	452,929	542,699	668,803	769,330	851,453	855,348
% of all ED visits	11.8%	12.9%	13.2%	13.6%	15.3%	16.7%	17.3%	16.9%
Rate per 100,000 population	102.3	131.6	151.8	180.2	219.9	250.8	275.3	274.5
Cocaine								
number of ED visits	475,425	483,865	548,608	553,535	482,188	422,902	488,101	505,224
% of all ED visits	18.7%	16.1%	15.9%	13.8%	11.0%	9.2%	9.9%	10.0%
Rate per 100,000 population	162.4	163.7	183.9	183.8	158.6	137.9	157.8	162.1
Alcohol								
number of ED visits	674,914	527,198	577,525	634,663	656,911	658,263	687,574	724,306
% of all ED visits	26.6%	17.5%	16.8%	15.9%	15.0%	14.3%	14.0%	14.3%
Rate per 100,000 population	230.5	178.4	193.6	210.7	216.0	214.6	222.3	232.5

Source: (Substance Abuse and Mental Health Services Administration, 2013).

Table 5
National survey on drug use and health (NSDUH): Lifetime use of various drugs among persons aged 12 and older, 2009–2015.

	2009	2010	2011	2012	2013	2014	2015
Psilocybin							
% lifetime	8.4%	8.3%	8.1%	8.1%	8.7%	8.5%	8.5%
% past year	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pain Relievers							
% lifetime	14.0%	13.8%	13.3%	14.2%	13.5%	13.6%	10.3%[a]
% past year	4.9%	4.8%	4.3%	4.8%	4.2%	3.9%	4.7%[a]
Cocaine							
% lifetime	14.6%	14.7%	14.3%	14.5%	14.3%	14.8%	14.5%
% past year	1.9%	1.8%	1.5%	1.8%	1.6%	1.7%	1.8%
Alcohol							
% lifetime	82.8%	82.5%	82.2%	82.3%	81.5%	82.1%	81.0%
% past year	66.8%	66.4%	66.2%	66.7%	66.3%	66.6%	65.7%

N/A = not assessed.
[a] NSDUH metric was "non-medical use" from 2009 to 2014, but changed to "misuse" in 2015. Additionally, the focus of the survey shifted from lifetime to past-year (for most drugs) in 2015. SAMHSA has suggested that these methods changes may cause trend breaks for some drugs, including pain relievers. Thus, caution needs to be applied when comparing 2015 estimates to those from 2009 to 2014.
Source: (Substance Abuse and Mental Health Services Administration, 2017b)

"hallucinogens" other than LSD. The two substances most commonly identified in the class "hallucinogens" other than LSD, has been psilocybin or "shrooms." From 2006 to 2011, lifetime prevalence of high schoolers using hallucinogens other than LSD (of which psilocybin/shrooms comprise the largest proportion), stayed relatively stable around 5.0%, but from 2011 to 2016, lifetime prevalence has decreased from 4.9% to 3.0%. Past year use among high schoolers mirrored this trend, staying relatively stable from 2006 to 2011 (around 3.0–3.3%) and declining from 3.1% in 2011 to 1.8% in 2016. Among college students, lifetime prevalence of use of "hallucinogens" other than LSD has steadily declined in the past 10 years from 10.1% in 2006 to 6.6% in 2016. Among college students, past year prevalence for "hallucinogens" other than LSD has also steadily declined from 5.4% in 2006 to 3.0% in 2016. Among young adults aged 19–28, lifetime prevalence for "hallucinogens" other than LSD declined from 14.9% in 2006 to 10.6% in 2016. Among young adults aged 19–28, past year prevalence for "hallucinogens" other than LSD has declined from 3.8% in 2006 to 3.0 in 2016.

2.4.1.5. National Forensic Laboratory Information System (NFLIS). The NFLIS system of the DEA is based on results from drug chemistry analyses conducted by state, local and federal forensic laboratories, from drug seizures by law enforcement. It is not a measure of human use, abuse, overdose or effects but rather is intended to provide information about what substances are being found in drug seizures (also known as "busts" or "raids") across the country (Drug Enforcement Administration Diversion Control Division, 2016). As shown in Table 6, the estimated number of total drug reports for psilocin/psilocybin has slightly declined from a high of 0.30% of total drug reports in 2010 to staying relatively stable from 2013 to 2015 (0.27% of all drug reports in 2013 and 0.26% of all drug reports in 2014 and 2015), however these rates are so small in comparison to other substances that interpretation must be made with caution.

2.4.1.6. American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS). As shown in Table 7, from 2007 to 2015, there were 5559 case mentions of psilocybin and psilocin reported to the National Poison Data System (NPDS). A mention indicates that the substance was associated with, but not necessarily the cause of, a reported suspected poisoning. Of these 5559 mentions, there was one death, in 2012. Whether this death was the result of psilocybin use or other concomitant drug use is unknown. Case reports mentioning psilocybin and psilocin have decreased from 773 reports in 2007 to 473 in 2015.

2.4.2. A note on "microdosing"

Psychedelic "microdosing," which involves use of very low, subperceptual, doses of psychedelics, has recently received attention in popular press articles and books (Fadiman, 2011; Koebler, 2015; Malone, 2016; Waldman, 2017). Although popular attention to microdosing is relatively new, Albert Hofmann discussed the medical potential of using very low doses of LSD for antidepressant effects as early as 1976 (Horowitz, 1976). Six percent of individual responding to a drug-related survey indicated having microdosed with LSD at least once in their lifetime (Global Drug Survey, 2017). However, nothing is currently known about the population-level prevalence of psychedelic microdosing, nor about microdosing of psilocybin mushrooms among psychedelic users. Given the substantial variability in psilocybin-content in mushrooms (Bigwood and Beug, 1982), one risk of microdosing with mushrooms is accidentally consuming a higher psilocybin dose than intended, resulting in strong and possibly overwhelming psychological effects in a dangerous or otherwise problematic environment, for example, while driving or working.

Table 6
National Forensic Laboratory Information System (NFLIS): Estimated percentage of total drug reports submitted to laboratories for various drugs, 2010–2015.

Drug	2010	2011	2012	2013	2014	2015
Psilocin/Psilocybin	0.30%	0.31%	0.31%	0.27%	0.26%	0.26%
Cocaine	21.44%	20.10%	16.54%	15.63%	14.10%	13.95%
Heroin	6.44%	7.21%	8.11%	9.85%	10.83%	12.12%
Oxycodone	3.56%	3.61%	3.40%	2.96%	2.85%	2.70%
Hydrocodone	2.81%	2.82%	2.66%	2.41%	2.19%	1.76%
Buprenorphine	0.61%	0.66%	0.73%	0.78%	1.01%	1.16%
MDMA	1.48%	0.78%	0.37%	0.31%	0.32%	0.33%

Sources: (Drug Enforcement Administration Diversion Control Division, 2011, 2012, 2013, 2014, 2015, 2016)

2.5. Factor 5: The scope, duration, and significance of abuse

There is an extensive history that provides important insights concerning patterns of psilocybin, LSD and other classic psychedelic use, abuse, and place in culture in the US and globally. Unlike, LSD, psilocybin is not a new molecular entity but rather is a naturally occurring substance that has been used ritualistically for at least hundreds and likely thousands years in Central and South America and possibly Africa and Europe (Akers et al., 2011; de Borhegyi, 1961; Lowy, 1971; Samorini, 1992; Schultes, 1969; Schultes et al., 2001; Truttman, 2012), with an apparently revered place in many cultures through history (Schultes et al., 2001). By way of contrast, alcohol, cocaine, opioids, and tobacco also have histories of use dating thousands of years, but these substances were recognized as addicting and harmful to the lives of many users for centuries (Corti, 1931; Crocq, 2007; Lewin, 1998; Rush, 1808; Terry and Pellens, 1970). As discussed in the foregoing citations, many users of these classic substances of abuse developed patterns of daily use that interfered with social and occupational functioning and caused harm to users. Moreover, with these drugs abstinence often came with great difficulty and was sometimes associated with sickness. Such sickness was eventually recognized as part of a withdrawal syndrome that contributed to the persistence of chronic daily use (Koob and Le Moal, 2006; O'Brien, 2011). These substances are recognized by the US National Institute on Drug Abuse (NIDA), and World Health Organization as prototypic substances of abuse that produced frequent self-administration and are often accompanied by some level physical dependence (withdrawal and tolerance) and lead to the clinical syndrome termed addiction in general communications, and substance use disorders or dependence in technical communications (American Psychiatric Association, 2013; National Institute on Drug Abuse, 2016; World Health Organization, 1993).

In contrast, whereas many experts (Gable, 1993, 2004) and expert organizations including NIDA and the DEA recognize psilocybin as a drug of abuse, they universally differentiate it from drugs that cause dependence/addiction and carry a high risk of overdose and harm. For example, NIDA Drug Facts website describes LSD and psilocybin type classic psychedelics as not addicting in contrast to NMDA antagonist phencyclidine (PCP) which may be considered an addicting "hallucinogen," broadly speaking. See Table 1.

The characterization of psilocybin as a substance with high abuse potential is based largely on social lore, sensationalized media coverage, and misinformation and misunderstanding about the actual risk of dependence and harms during the 1960s. This coincided with nonmedical use of classic psychedelics, primarily LSD, by the public in the 1960s (British Psychological Society, 2014; Costandi, 2014; Hofmann, 1980; Penner, 2015; Pollan, 2015). There is no question that such use involved motivation for intoxicating effects, and frequently involved co-administration of other substances. Furthermore, even though medical use by experienced practitioners had shown these drugs to be remarkably safe, use in the population for nonmedical reasons, often in high doses, in combination with other drugs, and in unsafe environments, led to highly sensationalized adverse consequences that contributed to the characterization of these substances as dangerous and highly abusable and ultimately in their placement in Schedule I of the CSA when it was codified in 1970. See further discussion in Belouin and Henningfield in this journal issue and Hofmann, 1980.

Scientific and medical studies, and US national surveillance systems yield a different characterization of psilocybin use, abuse, and risks than the 1960s media accounts as summarized in this factor and other factors. The scientific evidence confirms that there has been abuse and supports regulation as a controlled substance, however, that actual risk of dependence and harm associated with psilocybin has been estimated to be among the lowest of all major substances of abuse and dependence over the past several decades by several expert analyses, and lines of evidence evaluated in this factor and other factors of the CSA. For example, in a comparative overview of the dependence potential and acute toxicity of psychoactive substances, Gable concluded that psilocybin carried a lower risk of dependence than caffeine and among the lowest risks of death of all major substance abuse categories including cannabis (Gable, 1993). In a subsequent analysis using different methods Gable again found that psilocybin was amongst the least physiologically toxic drugs (Gable, 2004).

Similarly, Nutt, King, Saulsbury and Blakemore developed an instrument to assess drug harms and misuse that considered "physical" and "social" harm and dependence risk, and had a group of UK drug experts rank a large group of licit and illicit drugs (Nutt et al., 2007). Heroin, cocaine, sedatives and alcohol were ranked highest in overall harm. Although psilocybin was not specifically evaluated, the related drug LSD was ranked among the drugs with the lowest harm. This general approach was extended to use a more advanced decision-making approach, and included 16 specific criteria for evaluation by experts in the United Kingdom (Nutt et al., 2010). Alcohol was ranked most harmful with an overall harm score of 72 out of a possible 80, followed by heroin (overall harm score of 55 out of 80) and crack cocaine (overall harm score of 54 out of 80); the lowest overall score, as show in Fig. 3, was assigned to "mushrooms, with an overall harm score of 6 out of 80.

A large survey of 1501 UK drug users (Morgan et al., 2010) assessed ratings of harms for the drugs previously examined by the UK drug experts in Nutt et al. (2007). Although psilocybin was not assessed, LSD was ranked relatively low in harm among other drugs (Morgan et al., 2010). In a similar study (Carhart-Harris and Nutt, 2013), experienced drug users rated harms to "self" and to "others." The ratings by substance users and experts were overall similar, placing LSD among the lowest in harm to self and others with psilocybin-containing mushrooms receiving the lowest ratings (Carhart-Harris and Nutt, 2013). A study utilizing Dutch experts, using a framework based on that developed by Nutt and colleagues (Nutt et al., 2007), similarly concluded psilocybin-containing mushrooms to be the least harmful of all licit and illicit drugs examined, both to the individual and to the population (van Amsterdam et al., 2010). In turn, similar findings were obtained by 40 European Union addiction experts who scored 20 drugs on 16 factors related to harm (van Amsterdam et al., 2015). As shown in Fig. 4, harm ratings at the population and individual level were among the lowest for "magic mushrooms" among all substances that were evaluated.

Lending confidence to these various assessments of drug harm rankings is the remarkable correspondence among them. Specifically, using the drugs in common between studies, the correlation between Nutt et al. (2007) expert rankings and the Nutt et al. (2010) expert rankings were strong (Pearson's $r = 0.70$) despite

Table 7
American association of poison control centers' (AAPCC) national poison data system (NPDS), 2007–2015.

Drug		2007	2008	2009	2010	2011	2012	2013	2014	2015
Mushrooms: Hallucinogenics (Psilocybin and Psilocin)										
	# of Case Mentions	773	758	727	643	633	593	476	484	473
	# of Single Exposures	609	574	565	478	462	409	342	335	311
	Unintentional	83	82	59	74	40	44	50	49	32
	Intentional	511	479	495	394	408	350	285	266	266
	No Outcome	40	37	33	23	27	24	38	23	18
	Minor Outcome	112	92	111	92	104	69	64	83	75
	Moderate Outcome	257	248	243	193	187	180	142	142	137
	Major Outcome	9	9	11	6	4	8	5	7	5
	Death	0	0	0	0	0	1	0	0	0
Cocaine										
	# of Case Mentions	7634	6351	5293	5130	5485	4850	4749	4289	4738
	# of Single Exposures	2748	2075	1707	1582	1597	1345	1265	1171	1160
	Unintentional	281	261	184	162	168	140	133	105	127
	Intentional	2323	1695	1448	1329	1327	1133	1041	974	933
	No Outcome	488	419	349	234	231	191	197	175	195
	Minor Outcome	301	281	264	248	245	219	213	195	189
	Moderate Outcome	649	474	431	426	435	372	313	343	320
	Major Outcome	140	121	88	90	101	70	77	60	65
	Death	20	18	6	10	34	28	20	9	7
Codeine										
	# of Case Mentions	974	965	2056	1993	2054	1953	1935	1709	1824
	# of Single Exposures	629	616	1550	1501	1542	1467	1395	1254	1327
	Unintentional	499	449	1307	1270	1280	1215	1164	1049	1073
	Intentional	90	109	163	152	186	163	160	133	185
	No Outcome	158	123	413	409	403	389	364	345	332
	Minor Outcome	84	71	176	155	192	177	166	148	182
	Moderate Outcome	13	17	27	31	26	33	28	29	30
	Major Outcome	1	1	5	1	3	1	2	5	3
	Death	0	0	0	0	0	0	2	0	0
Hydrocodone Alone or in Combination[a], [b]										
	# of Case Mentions	–	–	–	316	1986	1989	1943	1956	1853
	# of Single Exposures	–	–	–	193	1089	1065	974	989	862
	Unintentional	–	–	–	116	675	698	604	646	538
	Intentional	–	–	–	59	297	247	271	243	234
	No Outcome	–	–	–	26	190	203	157	188	163
	Minor Outcome	–	–	–	47	246	215	188	211	161
	Moderate Outcome	–	–	–	14	67	51	63	47	46
	Major Outcome	–	–	–	0	10	3	2	2	2
	Death	–	–	–	0	1	0	0	4	1
Oxycodone Alone or in Combination[c]										
	# of Case Mentions	6515	7692	8065	9157	8963	8460	7742	7740	8170
	# of Single Exposures	3340	3741	3803	4278	3973	3644	3363	3300	3506
	Unintentional	1667	1980	1945	2102	1886	1820	1806	1763	1912
	Intentional	1271	1415	1463	1746	1700	1449	1231	1286	1319
	No Outcome	488	700	621	700	659	657	656	649	745
	Minor Outcome	560	615	714	804	758	673	655	782	775
	Moderate Outcome	260	289	368	478	469	409	387	397	431
	Major Outcome	78	85	91	112	108	105	90	81	109
	Death	9	11	8	12	37	26	20	15	13
Alcohol (Ethanol Beverages)										
	# of Case Mentions	47202	50919	51909	51549	53021	54445	50763	49305	51811
	# of Single Exposures	8668	8560	9937	9307	9166	9753	7954	6026	6761
	Unintentional	2428	2496	2640	2381	2371	2363	2218	2076	2190
	Intentional	5668	5512	6729	6223	6169	6738	5099	3340	3947
	No Outcome	1010	1153	1124	894	880	694	706	662	704
	Minor Outcome	1280	1174	1570	1498	1446	1567	1220	984	1237
	Moderate Outcome	915	935	1074	1099	1062	1221	1162	1021	1127
	Major Outcome	185	185	202	225	208	220	234	219	260
	Death	5	20	8	21	71	111	79	15	20

[a] Excluding Combination Products with Acetaminophen, Acetylsalicylic Acid or Ibuprofen.
[b] NFLIS started reporting Hydrocodone alone or in combination in 2010.
[c] Excluding Combination Products with Acetaminophen or Acetylsalicylic Acid.
Sources: (Bronstein et al., 2008, 2009, 2010, 2011, 2012; Mowry et al., 2013, 2014, 2015, 2016)

methodological differences (Nutt et al., 2010). The van Amsterdam et al. (2010) Dutch expert rankings and Nutt et al. (2010) UK expert rankings were also strongly correlated (Pearson's r: individual harm: 0.80, population harm: 0.84). The correlation between the UK drug user rankings in the Morgan et al. (2010) study and the UK expert rankings in Nutt et al. (2007) were strong (Pearson's $r = 0.90$) (Morgan et al., 2010). The correlation between the UK drug user rankings in the Carhart-Harris and Nutt (2013) study were

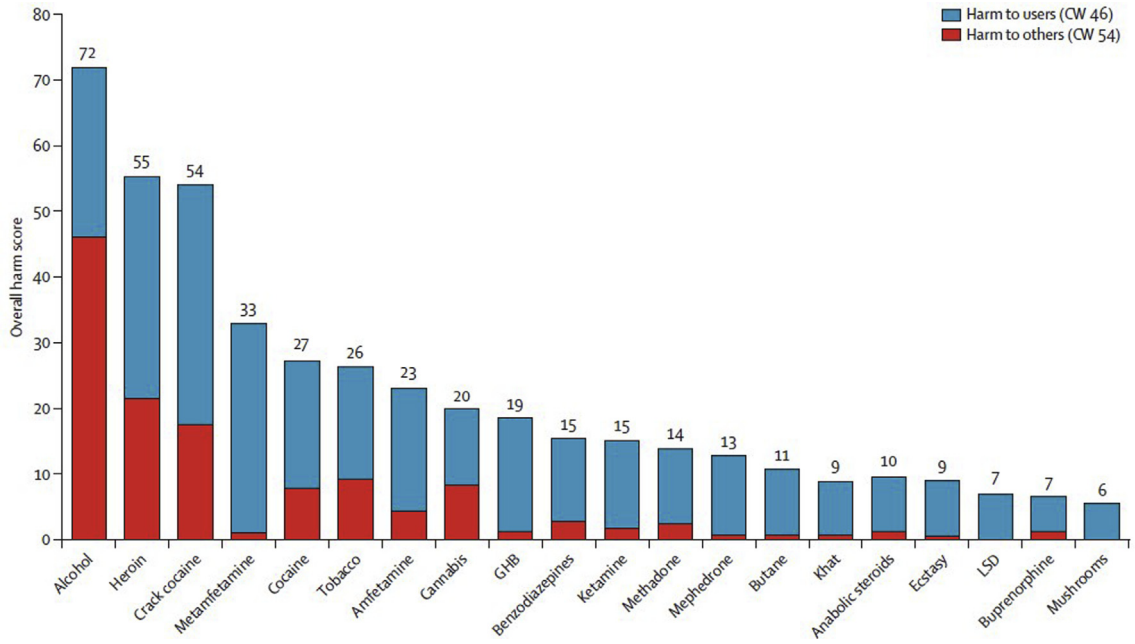

Fig. 3. Normalized ratings of harm potential of psilocybin ("mushrooms") relative to other drugs as rated by experts in the United Kingdom using on a multidimensional scale. Drugs are ranked by overall harm from left (most harmful) to right (least harmful), with harm to users (blue) and harm to others (red) shown separately. Abbreviations: CW = cumulative weight, GHB = gamma-hydroxybutyric acid (Figure from Nutt et al., 2010, Fig. 2).

strongly correlated with both of UK expert rankings (Nutt et al., 2010: User harms Spearman's rho = 0.90, harm to others Spearman's rho = 0.76) and the Dutch expert rankings (van Amsterdam et al., 2010) (Individual level: Spearman's rho = 0.93; Population level: Spearman's rho = 0.94) (Carhart-Harris and Nutt, 2013). The rankings of European Union addiction experts showed remarkably high correlations to UK experts (Nutt et al., 2010; van Amsterdam et al., 2015) (Overall harm: Pearson's r = 0.99). Collectively, these studies suggest strong international, cross-laboratory consensus, across academics, clinicians, and drug users themselves, regarding the relatively low harm potential of psilocybin compared to other drugs of abuse.

An evaluation of the harm-potential of psilocybin-containing mushrooms use, sanctioned by the Minister of Health of the Netherlands, "concluded that the physical and psychological dependence potential of magic mushrooms was low, that acute toxicity was moderate, chronic toxicity low and public health and criminal aspects negligible" (van Amsterdam et al., 2011). Further, the evaluation concluded that while "the use of magic mushrooms is relatively safe as only few and relatively mild adverse effects have been reported," the most harmful instances of use tended to involve the combination of other drugs including alcohol with mushrooms, and suboptimal settings such as the absence of a sober companion.

An important evaluation of the comparative epidemiology of dependence across a broad range of substances, including "psychedelics" was performed by Anthony, Warner and Kessler using data from the National Comorbidity Survey (Anthony et al., 1994). With respect to the rank ordering of the risk of transition from "drug use" to "dependence" they concluded as follows: "For both men and women, and for all but the oldest age group of drug users, tobacco and heroin were top ranked; psychedelic drugs (defined in report as "e.g., LSD, peyote, mescaline" which presumably would have included psilocybin) and inhalants were at the bottom." (Anthony et al., 1994). The inhalant results are unfortunately difficult to interpret because "inhalant" included compounds that widely varied in mechanism of action and related harms, from volatile solvents such as gasoline to nitrous oxide.

2.6. Factor 6: Risk to public health

Risks to public health can be estimated by a variety of approaches that help capture consequences of use among users and to nonusers. Carbonaro et al. (2016) reported on an online survey of psilocybin users about their single most psychologically difficult or challenging experience after consuming mushrooms. Eleven percent reported putting her/himself or others at risk of physical harm. Greater estimated dose, duration and difficulty of the experience, and lack of physical comfort and social support, were all related to increased risk. Approximately three percent reported behaving in a physically aggressive or violent manner, and the approximately three percent reported receiving medical help. Including only individuals whose reference psilocybin exposure occurred more than a year before survey completion, approximately eight percent reported seeking treatment for persisting psychological symptoms. Three of the respondents reported their psilocybin use to be followed by the onset of enduring psychotic symptoms. Three respondents reported attempting suicide.

As discussed in Factor 2, the risk of overdose poisoning by psilocybin is low due to its low physiological toxicity. In addition, it is possible that the often undesirable effects of high doses of psilocybin (Griffiths et al., 2011; Johnson et al., 2012), combined with large variability in the psilocybin-content of mushrooms (Bigwood and Beug, 1982) may lead many users to be cautious about dosing. On the other hand, its well documented sensory altering and impairing effects suggest a potential concern for the safety of users and others. By way of contrast, more than 10,000 or almost one third of all driving-related deaths in 2015 involved alcohol (Centers for Disease Control and Prevention, 2017), in addition to more than 2000 alcohol overdose poising deaths (Centers for Disease Control and Prevention, 2015), and nearly 80,000 alcohol related liver disease deaths (National Institute on Alcohol Abuse and

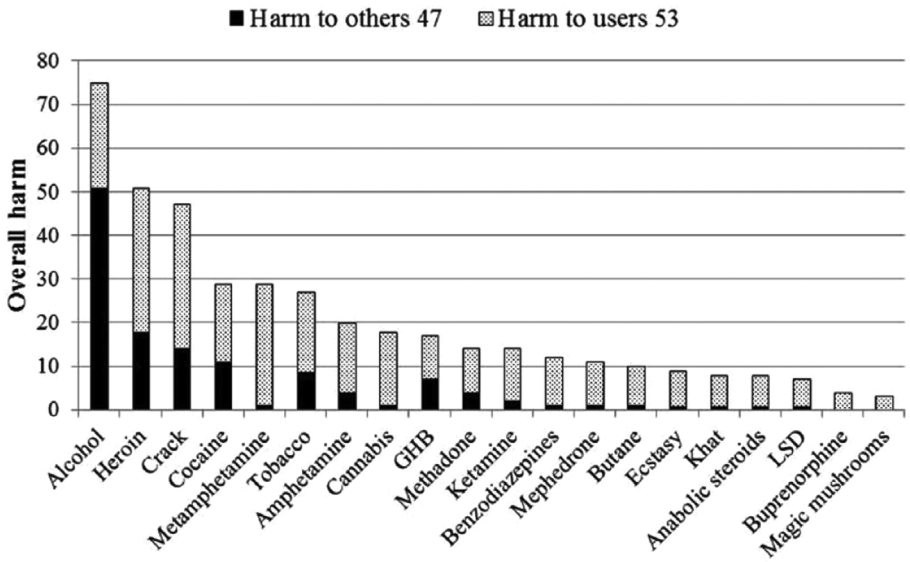

Fig. 4. Normalized ratings of harm potential of psilocybin ("magic mushrooms") relative to other drugs as rated by experts in the European Union using a multidimensional scale. Drugs are ranked by overall harm from left (most harmful) to right (least harmful), with harm to users (shaded texture) and harm to others (solid texture) shown separately (Fig. 2 from van Amsterdam et al., 2015).

Alcoholism, 2017). Recent trends suggest that an increasing fraction of highway motor vehicle accidents involve substances other than alcohol, including prescription drugs and possibly cannabis. The exception to this trend appears to be the category of "hallucinogens" (Rudisill et al., 2014). A plausible explanation is that the acute effects of classic psychedelics are so disrupting that persons under the influence are less likely to drive than those who are under the influence of intoxicating, sedating, and inhibition releasing substances that are more commonly associated with traffic accidents and fatalities. Another plausible contribution is the fact that psilocybin is typically used far less frequently than these other drugs which more readily lead to daily use and use disorders; therefore, there are fewer instances of drug intoxication involving driving and therefore fewer driving-related deaths.

Nonetheless, concerns about the safety of users and others have been voiced since early research with psilocybin and other psychedelics. Therefore, the relative rarity of apparent cases of classic psychedelic involved deaths does not mean that this should be of no concern (de Veen et al., 2017; Hofmann, 1980). Thus, despite an apparently low risk of addiction and physiological toxicity, there is concern about abuse because of potential adverse effects, including panic reactions, possible precipitation of enduring psychiatric conditions (i.e., psychotic disorders), and long-lasting visual perceptual disturbances. Importantly, these risks can be minimized by control of dose, setting, patient selection and other factors (Carhart-Harris and Nutt, 2013; de Veen et al., 2017; Johnson et al., 2008). What is reassuring, and at odds with one of the conditions for CSA Schedule I control ("There is a lack of accepted safety for use of the drug or other substance under medical supervision.") is that decades of experience and recent clinical research demonstrate that psilocybin can be used safely under medical supervision and the conditions of safe use are increasingly well-defined (Griffiths et al., 2016; Johnson et al., 2008; Ross et al., 2016).

It is likely that in the approval of psilocybin for therapeutic application, the FDA would not simply assume low risk, but rather would require that such serious but mitigatable concerns warrant a REMS to contribute to safe use and minimize unintended negative effects (U.S. Food and Drug Administration, 2015). Approval of drugs with REMS anticipates the likelihood that emerging clinical experience, further research, and the relatively high level of oversight and data collection provided by the REMS can support expansion of the conditions and indications for use and result in modifications of the REMS itself, as was the case for sodium oxybate (Xyrem®), the medication whose active pharmaceutical ingredient is the controversial substance commonly known as GHB (Carter et al., 2006, 2009; Johnson and Griffiths, 2013; McCormick et al., 2009; The Medical Letter, 2006; Wang et al., 2009). Data important in understanding the safety, mechanisms of action, and potential future indications for psilocybin-assisted treatment have included the treatment of substance use disorders (Bogenschutz et al., 2015; Garcia-Romeu et al., 2014; Johnson et al., 2012, 2014, 2017; Johnson and Griffiths, 2017; Nichols et al., 2017; Sessa and Johnson, 2015; Tupper et al., 2015), obsessive-compulsive disorder (Schindler et al., 2015), and cluster headaches (Matsushima et al., 2009; Sewell et al., 2006).

Ideally REMS are designed with knowledge gained from clinical trials to provide a basis for a plan that will contribute to beneficial effects and mitigate the risk of undesired effects. In this case there is knowledge that goes back to the 1950s efforts of Sandoz to ensure safe use by health care providers and the 21st century clinical trials have carefully designed and documented their programs to minimize unintended consequences. Furthermore, history and clinical research indicate that adverse events are not random but are related to controllable factors that can be addressed in labeling and by the requirement of elements to assure safe use (ETASU) of REMS that would likely be required by the FDA given (a) the 1960s history that did include problems, and (b) the apparent ability to minimize problems by following protocols employed in clinical research. In fact, information that would contribute to the development of a REMS is already emerging from recent clinical safety and efficacy trials.

2.6.1. Potential public health benefits

Risk to public health and overall public health impact must include consideration of benefits in order to provide a balance risk to benefit analysis. This concept has received increasing attention from the FDA in recent years. For example, in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) Section X,

is entitled “Enhancing Benefit-Risk Assessment in Regulatory Decision-Making.” This section required the FDA to “develop a five-year plan to further develop and implement a structured benefit/risk assessment in the new drug approval process” and “An evaluation plan to ascertain the impact of the benefit-risk framework in the human drug review process. The evaluation will consider the utility of the framework in facilitating decision-making and review team discussions across disciplines, risk management plan decision-making, training of new review staff, and communicating regulatory decisions. In particular, the evaluation will consider the degree to which the framework supports or facilitates balanced consideration of benefits and risks, a more consistent and systematic approach to discussion and decision-making, and communication of benefits and risks.” (U.S. Food and Drug Administration, 2012). The plan included holding two public workshops addressing benefit-risk considerations in drug regulation, one of which was held September 18, 2017 (U.S. Food and Drug Administration, 2017b).

The importance of public health benefits in drug scheduling decision-making is not new but its prominence seems to be increasing and in fact, the standard for evaluation of new tobacco products and for potential approval of some harm reduction tobacco products as “Modified Risk Tobacco Products” invokes a public health standard and not an efficacy standard by the 2009 Family Smoking Prevention and Tobacco Control Act (U.S. Congress, 2009). Nicotine is a drug that meets criteria for placement in Schedule III of the CSA (if marketed as a drug but not in the form of tobacco products which are exempted from CSA scheduling along with alcoholic beverages by the CSA) but the potential public health benefits of nicotine were prominent in the decision by the FDA not to recommend scheduling upon approval of nicotine gum in 1985, and in 1996 not to recommend scheduling of a nasal nicotine product that clearly met criteria for such control (Henningfield et al., 2016; U.S. Food and Drug Administration, 1996). Similarly, public health considerations were prominent in the FDA's resistance to reschedule low-dose hydrocodone plus acetaminophen products from Schedule III to Schedule II (Anson, 2014; Coleman, 2015).

In this context, it is important to recognize the potential public health benefits of psilocybin and to avoid unduly restrictive scheduling that would pose an unnecessary barrier to potential life-saving and public health enhancing access. For example, placement in Schedule II is intended to pose high barriers to patient prescribing by health care providers and access by patients, and this was a consideration in advocacy by the FDA, pain patient advocacy organizations, and many people with pain in sustaining the low dose acetaminophen combination form of hydrocodone in Schedule III as discussed above (Coleman, 2015).

As discussed in the summaries of analyses of Factors 4 and 5 in this article and earlier in this section, the overall risks to public health posed by illicit psilocybin are low compared to most scheduled drugs and certainly lower than most Schedule II and III drugs. Clinical studies of psilocybin suggest that the public health risk of an approved medicine would be lower still due to the restrictions on its access imposed by distribution only through pharmacies and potentially at least initially limited to a single central pharmacy provider if that was recommended as part of its REMS program (Griffiths and Johnson, 2015).

The potential medical and public health benefits of medicinal psilocybin were demonstrated by research up until the 1960s, and with some resurgence beginning in the 1990s. The clinical development program for psilocybin as a potential medicine as for the treatment of depression and anxiety and to improve quality of life in patients with life-threatening cancer diagnoses (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), provides more recent data, from studies that are intended to meet FDA standards for Phase 1 and 2 studies to support an eventual NDA. In summary, Grob et al. assessed the effects of one-time psilocybin (14mg/70 kg doses) using a double-blind, placebo-controlled design, with administration in a therapeutic setting in patients with life-threatening illnesses including cancer (Grob et al., 2011). There were reductions in measures of trait anxiety and depressed mood that persisted through the 6-month follow-up observation. There were no serious adverse events. Carhart-Harris et al. conducted an open label study of 10 and 25 mg doses of psilocybin administered 7 days apart in a supportive setting in patients with treatment-resistant depression. This demonstrated strong reductions in measures of depression at 1 week and 3 months by the 16-item Quick Inventory of Depressive Symptoms, with no serious adverse events (Carhart-Harris et al., 2016b).

The most rigorous study of psilocybin for treatment of depressed mood and anxiety in severely distressed cancer patients was by Griffiths et al. (2016), as described under Factor 2. Acute effects during the sessions were described (see Fig. 2). As shown in Fig. 5, the therapeutic benefits of the high dose of psilocybin (~0.314 or ~0.429 mg/kg) were profound and persistent as reported by both patients and observers. The overall rates of clinician-rated therapeutic effects at 6 months were 78% for depression and 83% for anxiety. Ross et al. conducted a study that was generally similar to that by Griffiths et al., with the most important difference being the use of small doses of niacin as an active placebo instead of low doses of psilocybin (Griffiths et al., 2016; Ross et al., 2016). Ross et al. also found robust acute and sustained antidepressant effects by psilocybin. Ross et al. and Griffiths et al. have assisted a nonprofit program that has been coordinated by the Heffter Research Institute (Heffter Research Institute, 2017) and Usona Institute (Usona Institute, 2017) which are working together to sponsor the development of psilocybin for approval as a medicine by the FDA. These studies include measures of mood enhancement in patient populations that are not discussed in Factor 1 (regarding euphoriant effects) because the relevance of persisting mood improvement in depressed and anxious patients to abuse potential is not clear (Griffiths et al., 2016).

Non-therapeutic laboratory studies of psilocybin in healthy volunteers also suggest positive persisting effects of psilocybin. Two studies administering doses of up to ~0.429 mg/kg to healthy volunteers showed increased participant ratings of well-being or life satisfaction (Griffiths et al., 2008, 2011) 14 months after psilocybin administration. Data pooled across these studies showed an increases in personality over a year after psilocybin administration (MacLean et al., 2011). A recent, large laboratory study examining the interactive effects of psilocybin and spiritual practices (including meditation) in 75 healthy volunteers showed high-dose psilocybin (~0.286 and ~0.429 mg/kg in two separate sessions) to cause significant increases in ratings of interpersonal closeness, gratitude, and life meaning/purpose 6 months after psilocybin administration, suggesting persisting improvements prosocial traits and psychological functioning (Griffiths et al., 2018).

Larger, population- and cohort-based studies are consistent with findings from these experimental investigations. For example, Hendricks et al. tested the relationships of classic psychedelic use and psilocybin use per se with psychological distress and suicidality among over 190,000 adult respondents pooled from years 2008 through 2012 of the NSDUH (Hendricks et al., 2015a, 2015b). They found that lifetime classic psychedelic use was associated with a reduced odds of past month psychological distress (aOR = 0.81), past year suicidal thinking (aOR = 0.86), past year suicidal planning (aOR = 0.71), and past year suicidal attempt (aOR = 0.64), with these results extending to psilocybin per se. Lifetime illicit use of other drugs was, by and large, associated with an increased odds of

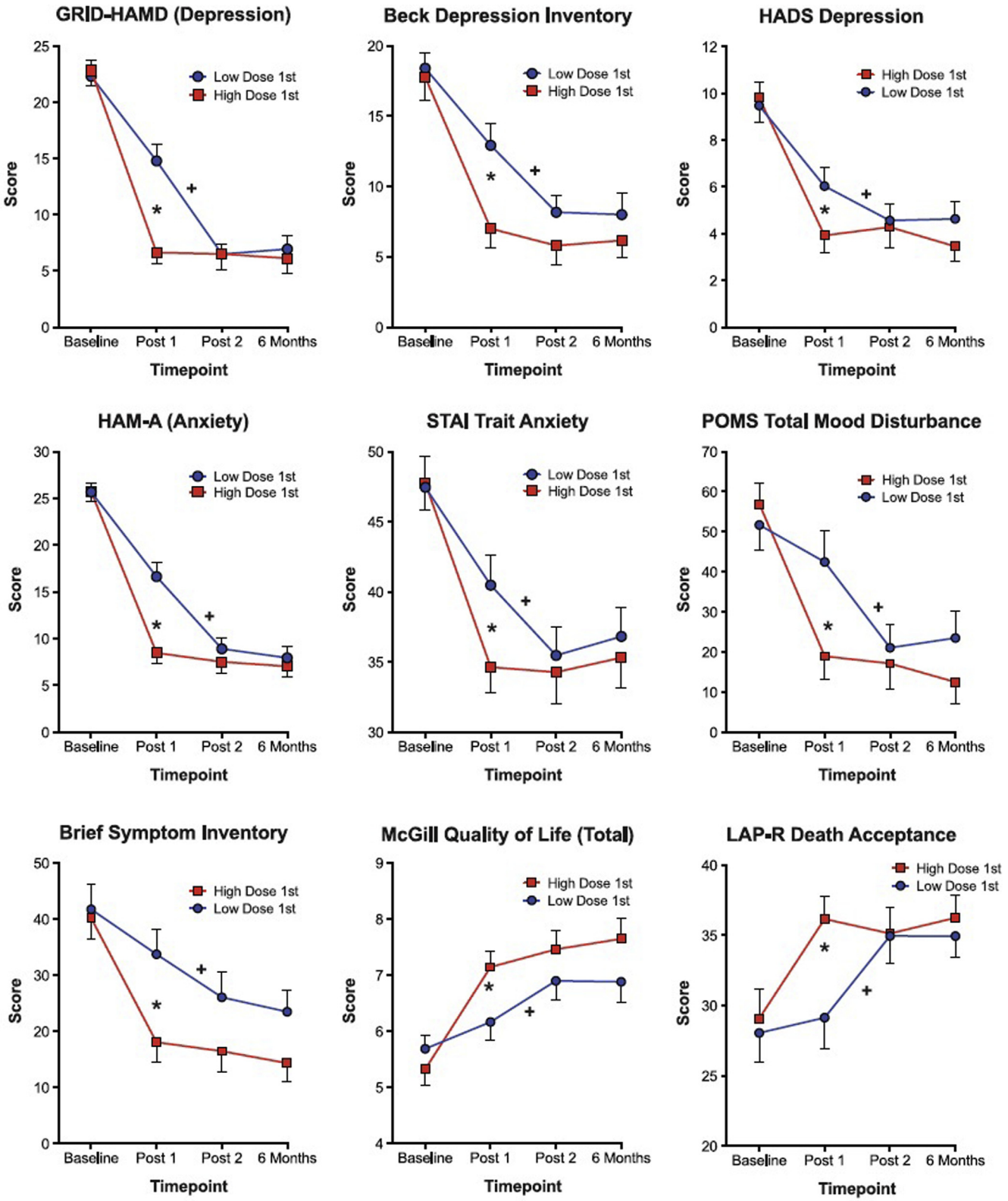

Fig. 5. Persisting effects of psilocybin on depression- and anxiety-related outcome measures Outcomes were measured at baseline (pre-psilocybin), post session 1 (5 weeks after the first psilocybin session), post session 2 (5 weeks after the second psilocybin session), and the 6-month follow-up (n = 25, 25, 24, and 22 at baseline, post session 1, post session 2, and 6 months, respectively). Each panel shows the mean (±SEM) scores for two groups: The "Low Dose 1st" group received a low, placebo-like (~0.014 or ~0.043 mg/kg) dose of psilocybin in Session 1, and a moderately-high (~0.314 or ~0.429 mg/kg) dose of psilocybin in Session 2; the "High Dose 1st" group received the doses in the opposite order. Stars show a significant difference between the two groups at post session 1 by planned comparison ($p < 0.05$). Crosses show a significant difference between the post session 1 and post session 2 times in the Low-Dose-1st group by planned comparison ($p < 0.05$). (Figure from Griffiths et al., 2016, Fig. 3).

these outcomes. Building on these findings, Argento et al. (2017) found that psychedelic drug use, broadly defined (i.e., not restricted only to 5HT2A agonists but also including MDMA) prospectively predicted a reduced likelihood of suicide ideation or attempts among 290 marginalized Canadian women (aHR = 0.40). Moreover, consistent with pilot studies of psilocybin-assisted psychotherapy for drug dependence (Bogenschutz et al., 2015; Johnson et al., 2014), Pisano et al. found that lifetime classic psychedelic use was associated with a reduced risk of past year opioid dependence (weighted risk ratio = 0.73) and past year opioid abuse (weighted risk ratio = 0.60) among over 44,000 illicit opioid users who completed the NSDUH in years 2008 through 2013 (Pisano et al., 2017). Finally, a growing literature suggests protective effects for individuals in the criminal justice system, who suffer from numerous comorbid psychopathologies including depression, anxiety, and drug dependence that exacerbate criminal behavior. Hendricks et al. found that naturalistic "hallucinogen" use predicted a reduced likelihood of recidivism among over 25,000 individuals under community corrections supervision with a history of substance involvement (aOR = 0.60) (Hendricks et al., 2014) and Walsh et al. found that naturalistic "hallucinogen" use predicted reduced arrest for intimate partner violence among 302 jail inmates (aOR = 0.62) (Walsh et al., 2016). Of course, as "hallucinogens" are a broader class of substance that includes classic psychedelics such as psilocybin in addition to other substances, these studies were not able to test the unique relationships of classic psychedelics or psilocybin in particular with criminal behavior. Toward that end, Hendricks et al. (2018) evaluated the associations of classic psychedelic use, and psilocybin use per se, with criminal behavior among over 480,000 adult respondents pooled from years 2002 through 2014 of the NSDUH. They found that lifetime classic psychedelic use was associated with a reduced odds of past year larceny/theft (aOR = 0.73), past year assault (aOR = 0.88), past year arrest for a property crime (aOR = 0.78) and past year arrest for a violent crime (aOR = 0.82). Results also were consistent with a protective effect of lifetime psilocybin use for past year antisocial behavior. Lifetime illicit use of other drugs was largely associated with an increased odds of these outcomes.

To be clear, it is not a conclusion of this review that psilocybin or other psychedelics should currently be recommended as a general or blanket approach for the prevention of suicide or other behaviors and conditions discussed in this section. Nor is it proposed that approval of psilocybin for depression and anxiety disorders related to advanced cancer diagnosis will translate to reduced suicide or other problems at the population level in the near term, if ever. In part this is because self-selection and other factors may contribute to the population level effect. Furthermore, psilocybin and related substances can produce adverse effects that were documented by Hofmann in the 1940s and since, and the risks of such adverse events can be minimized by appropriate protocols, conditions for use, dosing and other factors. However, in the evaluation of the potential public health effects, the data suggest that psilocybin is overall more likely to contribute to public health improvement than to adversely affect public health. Taken together, the evidence suggest that, at least with respect to certain mental disorders, psilocybin appears to offer potential benefits to patients and little risk to public health (Belouin and Henningfield, 2018).

2.7. Factor 7: Psychic or physiological dependence liability

No apparent physiological dependence as evidenced by withdrawal symptoms has been documented in humans (clinical observations) or animals (laboratory studies), although tolerance has been observed (Abramson et al., 1960; Appel and Freedman, 1968; Isbell et al., 1961). For example, no withdrawal was reported following chronic psilocybin use in humans in ARC studies including a study by Isbell et al. (1961) of 19 participants that included up to 12 days of psilocybin (ascending up to 0.15 mg/kg or 0.21 mg/kg) followed by up to 13 days monitoring after termination of administration. With the exception of MDMA, which is distinct from classic psychedelics both in effects and primary pharmacological mechanism of action, the Fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM 5) does not include a diagnosis of withdrawal for "hallucinogens" (American Psychiatric Association, 2013). As concluded by O'Brien (2011), "Frequent, repeated use of psychedelic drugs is unusual, and thus tolerance is not commonly seen. Tolerance does develop to the behavioral effects of LSD after three or four daily doses, but no withdrawal syndrome has been observed" (O'Brien, 2011). The Isbell et al. (1961) study discussed above observed tolerance (decreased drug effect after chronic treatment) to all measured effects of psilocybin, some of which met statistical significance. Hollister reported on a single participant who was administered psilocybin on a daily basis for 22 days, with doses ranging from 1.5 to 27 mg per day, and noted strong tolerance, with minimal apparent effects, to 15 mg on day 22 (Hollister, 1961). After several weeks of abstinence the same 15 mg dose resulted in a robust and typical response, demonstrating a recovery from tolerance. Cross-tolerance occurs between psilocybin and LSD (Abramson et al., 1960; Appel and Freedman, 1968; Isbell et al., 1961).

2.8. Factor 8: Immediate precursor of substance controlled

Psilocybin is a prodrug to the active entity, psilocin, both of which are currently placed in Schedule I of the CSA.

3. Discussion

3.1. Summary and recommendation for CSA scheduling

All 8 factors and other lines of evidence taken together indicate the profile of a substance that is characterized by some level of abuse potential and potential risks. However, the findings do not support placement more restrictively than Schedule IV. The current placement in Schedule I is presently necessitated by the absence of FDA approval for a psilocybin containing medicine and Schedule I is the only Schedule into which substances of abuse can be placed that do not have an approved medical indication. However, it is the opinion of the authors of this review that the original placement of psilocybin was the result of a substantial overestimation of the risk of harm and abuse potential. The CSA stipulates that Schedule I is for substances with a high potential for abuse, lack of therapeutic approval, and that cannot be used safely in medicine. History of use and available scientific data show that the first criterion is questionable, and the third criterion is likely not true. The second of these criteria can only be negated by FDA approval of a psilocybin-containing products, but at this point the data suggest that the potential therapeutic benefits of psilocybin-assisted therapy are real, and of potential medical and public health significance.

Schedule placement is guided by an analysis of the 8 factors of the CSA that will be drafted by the FDA with input from NIDA. The 8-factor analysis contained in this review should be considered an abbreviated assessment of abuse potential as compared to what would be required by the FDA to accompany the submission of an NDA for approval of a psilocybin containing drug product. Furthermore, considerable additional study will yet be required to support the submission of a complete and reviewable NDA and its abuse potential assessment. This will include at least one major phase 3 clinical efficacy and safety trial that includes assessments relevant to abuse potential, additional Phase 1 and/or 2 clinical

studies, and possibly some animal testing (Calderon et al., 2017; Sellers et al., 2017). Thus data yet to be collected will influence the final scheduling proposal that will be made by the sponsor and, in turn by the FDA, NIDA, and DEA. Nonetheless, considerable data from animal self-administration and discrimination studies, and human abuse potential studies since the 1960s provide a substantial basis for the present preliminary evaluation. In contrast to Schedule III drugs and even to many drugs placed in Schedule IV, the reinforcing effects in preclinical studies are marginal. There is no clear evidence of physical dependence and withdrawal in preclinical or clinical studies, or among those who chronically used illicit products. Euphoriant effects can occur under limited circumstances but appear attenuated by dysphoric effects. The doses that pose a risk of acute poisoning death ("overdose") appear to be approximately 1000 times the likely highest clinical dose to be marketed, psychological dependence resulting in daily use appears rare, and all major drug surveillance systems reviewed in Factors 4, 5, and 6 of this analysis indicate rates of abuse, emergency department reports, and treatment seeking in youth and adults that are substantially lower than are evident for many Schedule IV drugs. It is possible, of course that subsequent study with larger populations and different designs in animals and humans, would yield different outcomes, but this review suggests that psilocybin would be appropriately placed in Schedule IV of the CSA if the FDA approves a psilocybin NDA.

The authors of this review recognize that opinions in the general population may differ substantially as it is clear that there remains a legacy of fear regarding psychedelics since the 1960s. The role of the 8-factor analysis of the CSA is to bring science to bear to support the foundation for scheduling, implications for other aspects of scheduling which are based on much of the same data. In particular, this means the labeling that will be specific to the label section, Drug Abuse and Dependence (section 9 of the drug labeling), and warnings including the possible requirement of a Boxed Warning (U.S. Food and Drug Administration, 2017d). As with all approved drug products, determination of safe and effective by the FDA does not mean without risk, and the conclusion that the science does not support scheduling more restrictive than IV does not mean no abuse or dependence risk.

3.2. Implications for research and policy

This analysis has implications for future research with psilocybin and for the possible development of related drugs. Perhaps most challenging and important is research to better understand the mechanisms of action of psilocybin and related drugs that can produce profound and very long lasting positive changes in mood and well-being in people who were resistant to standard care and approved medicines. Given the extent to which undertreated and treatment resistant mental and behavioral disorders, including mood, anxiety, and substance use disorders, remain serious problems at the personal and societal levels in the US and globally (Belouin and Henningfield, 2018), it could be concluded that the need for such research is urgent.

The dearth of therapeutic and mechanistic studies of psilocybin and other classic psychedelics over the past half-century does not stem from a lack of interest among psychologists, psychiatrists, pharmacologists and neuroscientists. Research has been and continues to be limited by the provisions of the CSA and the lack of prioritization of such research by potential federal funding agencies. As discussed elsewhere, the barriers to research imposed by Schedule I regulation are formidable and although they do not outright ban such research, the consequence has been that this area of science and potential clinical application has been greatly underresearched (Belouin and Henningfield, 2018; Nutt, 2015; Nutt et al., 2013; Scientific American Editors, 2014; Sinha, 2001; Spillane, 2004; Woodworth, 2011). Several of the key clinical studies have been primarily supported by private foundations rather than federal institutions such as NIH (Bogenschutz et al., 2015; Griffiths et al., 2016; Johnson et al., 2014; Ross et al., 2016).

The science of drug abuse potential assessment has evolved considerably in recent decades and this is evident in the FDA's 2017 guidance document, "Assessment of Abuse Potential of Drugs," that summarizes research strategies, and methods and discusses how these can be brought to bear to provide the regulatory science foundation for drug scheduling decisions. The application of this scientific approach to further evaluate the abuse potential of psilocybin provides an example of how this area of regulatory science has the potential to facilitate innovative therapeutic breakthroughs by replacing fear and misinformation with scientifically based conclusions and facts.

4. Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Roland Griffiths is on the Board of Directors of the Heffter Research Institute which supports psilocybin research and the potential development and submission of an NDA to the U.S. FDA.

Through Pinney Associates, Jack Henningfield has consulted and/or is presently consulting to the Heffter Research Institute and to the Usona Institute, which are supporting the development of psilocybin as a new medication to be submitted for approval by the U.S. FDA, as well as to other sponsors of central nervous system acting products concerning their abuse potential, appropriate regulation, and medicinal application.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuropharm.2018.05.012.

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Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function

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ABSTRACT

The purpose of this paper is to provide an integrative review and offer novel insights regarding human research with classic psychedelics (classic hallucinogens), which are serotonin 2A receptor (5-HT_{2A}R) agonists such as lysergic acid diethylamide (LSD), mescaline, and psilocybin. Classic psychedelics have been administered as sacraments since ancient times. They were of prominent interest within psychiatry and neuroscience in the 1950s to 1960s, and during this time contributed to the emergence of the field of molecular neuroscience. Promising results were reported for treatment of both end-of-life psychological distress and addiction, and classic psychedelics served as tools for studying the neurobiological bases of psychological disorders. Moreover, classic psychedelics were shown to occasion mystical experiences, which are subjective experiences reported throughout different cultures and religions involving a strong sense of unity, among other characteristics. However, the recreational use of classic psychedelics and their association with the counterculture prompted an end to human research with classic psychedelics in the early 1970s. We provide the most comprehensive review of epidemiological studies of classic psychedelics to date. Notable among these are a number of studies that have suggested the possibility that nonmedical naturalistic (non-laboratory) use of classic psychedelics is associated with positive mental health and prosocial outcomes, although it is clear that some individuals are harmed by classic psychedelics in non-supervised settings. We then review recent therapeutic studies suggesting efficacy in treating psychological distress associated with life-threatening diseases, treating depression, and treating nicotine and alcohol addictions. We also describe the construct of mystical experience, and provide a comprehensive review of modern studies investigating classic psychedelic-occasioned mystical experiences and their consequences. These studies have shown classic psychedelics to fairly reliably occasion mystical experiences. Moreover, classic-psychedelic-occasioned mystical experiences are associated with improved psychological outcomes in both healthy volunteer and patient populations. Finally, we review neuroimaging studies that suggest neurobiological mechanisms of classic psychedelics. These studies have also broadened our understanding of the brain, the serotonin system, and the neurobiological basis of consciousness. Overall, these various lines of research suggest that classic psychedelics might hold strong potential as therapeutics, and as tools for experimentally investigating mystical experiences and behavioral-brain function more generally.

Abbreviations: 25I-NBOMe, 4-Iodo-2,5-dimethoxy-N-[(2-methoxyphenyl)methyl]-benzeneethanamine; 2C-B, 2,5-Dimethoxy-4-bromophenethylamine; 5-HT_{2A}R, Serotonin 2A receptor; 5-MEO-AMT, 5-Methoxy-α-methyltryptamine; 5-MEO-DPT, 5-Methoxy-N,N-dipropyltryptamine; 5-MEO-DMT, 5-Methoxy-N,N-dimethyltryptamine; ACC, Anterior cingulate cortex; AIRFA, American Indian Religious Freedom Act; AMT, α-Methyltryptamine; BC, Before Christ; BOLD, Blood oxygenation level dependent; DAWN, Drug Abuse Warning Network; DEA, Drug Enforcement Administration; DMN, Default mode network; DMT, Dimethyltryptamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DXM, Dextromethorphan; ED, Emergency department; EEG, Electroencephalography; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; fMRI, functional magnetic resonance imaging; HD-SS, High-dose with standard support for spiritual-practice; HD-HS, High-dose with high support for spiritual-practice; kg, Kilogram; LD-SS, Low-dose with standard support for spiritual-practice; LPC, Lateral parietal cortex; LSA, Lysergic acid amide; LSD, Lysergic acid diethylamide; MDMA, 3,4-Methylenedioxymethamphetamine; MEG, Magnetoencephalography; MEQ30, 30-item Mystical Experience Questionnaire; MEQ43, 43-item Mystical Experience Questionnaire; mg, Milligram; MPFC, Medial prefrontal cortex; MRS, Magnetic resonance spectroscopy; MTF, Monitoring the Future; NAC, Native American Church; NMDA, N-Methyl-D-aspartate; NSDUH, National Survey on Drug Use and Health; PCC, Posterior cingulate cortex; PET, Positron emission tomography; sgACC, Subgenual anterior cingulate; SPECT, Single photon emission computed tomography; TAAR1, Trace amine-associated receptor 1; UDV, União do Vegetal; USDHHS, United States Department of Health and Human Services.

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Contents

1. Introduction

1.1. Classic psychedelics defined

Classic psychedelics (or classic hallucinogens) are psychoactive compounds that exert effects through agonist (including partial agonist) activity at the serotonin 2A receptor (5-HT_{2A}R). Substantial evidence suggests that 5-HT_{2A}R, which is a G-protein-coupled receptor, is the most important receptor underlying classic psychedelic effects (Nichols, 2016). For example, rat studies have shown for a variety of classic psychedelics that 5-HT_{2A}R antagonists block the ability of classic psychedelics to serve as discriminative stimuli (Glennon, Young, & Rosecrans, 1983; Glennon, Titeler, & McKenney, 1984). Human studies have also shown that 5-HT_{2A}R antagonism blocks the subjective and other effects of the classic psychedelic psilocybin (Kometer et al., 2012; Quednow, Kometer, Geyer, & Vollenweider, 2012; Kometer, Schmidt, Jancke, & Vollenweider, 2013; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998). Consistent with these findings, 5-HT_{2A}R knockout mice do not exhibit the head-twitch response, a characteristic rodent response to classic psychedelics (Halberstadt, Koedood, Powell, & Geyer, 2011).

Despite the primary role of 5-HT_{2A}R agonism, other receptor-level mechanisms also contribute to classic psychedelic effects. For example, 5-HT_{2C} receptors, and for certain classic psychedelics, 5-HT_{1A} receptors, play a role in classic psychedelic effects (Nichols, 2016; Halberstadt & Geyer, 2011). The effects of particular classic psychedelics also involve non-5-HT receptors, for example, at high doses LSD has dopaminergic and adrenergic effects (Kyzar, Nichols, Gainetdinov, Nichols, & Kalueff, 2017; Nichols, 2016). Multiple classic psychedelics activate trace amine-associated receptor 1 (TAAR1) (Bunzow et al., 2001; De Gregorio et al., 2016), suggesting the possibility that this receptor may contribute to classic psychedelic effects (Kyzar et al., 2017). However, the behavioral and subjective consequences of classic psychedelic activation of TAAR1 need to be investigated, and multiple drugs other than classic psychedelics (e.g., amphetamine) also activate TAAR1, suggesting TAAR1 activation may not underlie effects that are quintessential to classic psychedelics. Beyond receptor activation, classic psychedelics, but not a nonpsychoactive agonist of the 5-HT_{2A}R, have been shown to upregulate immediate early genes that encode for transcription factors, which in turn regulate multiple genes (González-Maeso et al., 2003). Many of the immediate early genes upregulated by classic psychedelics code for proteins with involvement at the synapse, likely with effects on synaptic structure in addition to neurotransmission, providing potential mechanisms underlying persisting as well as acute classic psychedelic effects (Kyzar et al., 2017).

Classic psychedelics fall within one of two general structural categories. One category includes variations on the structure of *tryptamine*. Examples include LSD, psilocybin, and dimethyltryptamine (DMT), a psychoactive compound present in the South American sacramental beverage *ayahuasca*. The second category includes variations on the structure of *phenethylamine*. One example is mescaline, the main psychoactive agent in the peyote (*Lophophora williamsii*), San Pedro (*Echinopsis pachanoi*) and Peruvian torch (*Echinopsis peruvianus*) cacti (Nichols, 2016). A variety of synthetic compounds not known to occur in nature also fall in the phenethylamine category (e.g., 2C-B, 25I-NBOMe). Indigenous cultures in the Western Hemisphere have used compounds from both structural classes in the sacramental use of ayahuasca, psilocybin-containing mushrooms, and mescaline-containing cacti. One analog of phenethylamine is methylenedioxymethamphetamine (MDMA), which causes psychoactive effects with only partial overlap with classic psychedelics, and which works primarily via serotonin release rather than 5-HT_{2A}R agonism (Nichols, Lloyd, Hoffman, Nichols, & Yim, 1982). Like MDMA, other drugs sometimes labelled as psychedelic (e.g., NMDA antagonists, anticholinergics, cannabinoids, salvinorin A, ibogaine) which are not classic psychedelics, will not be reviewed here because of their substantially differing mechanisms and effects. Although reviews with some overlap to the present manuscript have been published (e.g., Barrett & Griffiths, 2017; dos Santos et al., 2016; Johnson & Griffiths, 2017; Mahapatra & Gupta, 2017; Nichols et al., 1982; Patra, 2016), none of these provide detailed coverage of each domain of the present review (epidemiology, therapeutics, mystical experience, and brain network function).

1.2. Classic psychedelic effects

Perhaps the best description of a classic psychedelic is found in Grinspoon and Bakalar (1979, page 9) who define it as "A drug which, without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis." Classic psychedelics often cause extreme changes in subjective experience during acute drug action (Passie, Seifert, Schneider, & Emrich, 2002), encompassing complex changes in affective, cognitive, and perceptual domains (Griffiths, Richards, McCann, & Jesse, 2006; Griffiths et al., 2011; Preller & Vollenweider, 2016). One type of subjective experience referred to as mystical-type experience can be occasioned by administration of relatively high doses of classic psychedelics in optimal settings (Gasser et al., 2014; Griffiths et al., 2006, 2011; Pahnke, 1963; Pahnke, 1969; Pahnke & Richards, 1966; Richards, Rhead, Dileo, Yensen, & Kurland, 1977), and will be discussed in detail in a subsequent section.

The term "hallucinogen," which has been widely applied to classic psychedelics in scientific circles, is not ideal because these substances do not typically produce frank hallucinations, and this term, which connotes only perceptual effects, is an insufficient description of the often radical effects these drugs have on human consciousness and one's sense of self. Therefore, the term "hallucinogen" has fallen out of favor, with a re-emergence of the scientific use of the term "psychedelic" to refer to these substances (Nichols, 2016). The term "psychedelic," which means "mind-manifesting," was coined by the pioneering classic-psychedelic researcher Humphrey Osmond in 1957 (Dyck, 2006). As summarized later in this review, recent psychological and biological

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research indicates the accuracy of this term by suggesting this class of drugs to cause a non-ordinary and more variable form of consciousness that is less centered on one's normal sense of self, and that involves enhanced autobiographical recollection (Carhart-Harris et al., 2012a; Carhart-Harris et al., 2012b).

Classic psychedelic administration entails risks. These fall into three major categories. One that is relevant to any individual taking a sufficiently high dose of a classic psychedelic is an anxious, dysphoric, confusing, and, less commonly, delusional acute reaction, often referred to as a "bad trip" in colloquial language. Although these can be safely managed with safeguards in place within clinical research, these challenging experiences can potentially lead to accidents or other dangerous behavior in unsupervised settings (Carbonaro et al., 2016). Another risk is the exacerbation of psychotic disorders or instigation of a prolonged psychotic reaction. For cases in which initial psychotic reactions within the lifetime occur after taking a classic psychedelic, psychotic vulnerability is suspected, but it is not possible to determine if that individual would have eventually had a psychotic reaction or not if he/she had not been exposed to the drug (Grinspoon & Bakalar, 1979). Early survey research of investigators who had administered classic psychedelics to humans suggest that prolonged psychiatric reactions (>48 h) are limited to such vulnerable individuals, with only 1 case occurring among 1200 non-patient participants, and that single patient was an identical twin of a patient with schizophrenia. The same report found prolonged psychiatric reactions occurred at a rate of 1.8 per 1000 individuals for psychiatric patients. It also reported no suicide attempts for the 1200 non-patient participants, with suicide attempts and completed suicides occurring at respective rates of 1.2 and 0.4 per 1000 patients (Cohen, 1960). Drawing from multiple previous reports of studies conducted in the 1960s and 1970s, Abraham, Aldridge, and Gogia (1996) reported that rates of developing psychoses following the administration of LSD range from .08% to 4.6%, with higher rates among psychiatric patients. Screening of psychotic disorders and vulnerability is therefore an important safeguard against such psychiatric reactions (Johnson, Richards, & Griffiths, 2008). It should be noted that the acute anxious, dysphoric, confusing, and/or delusional reactions discussed above have sometimes been studied as psychosis symptoms, and therefore classic psychedelics have sometimes been considered to model psychotic symptoms (e.g., Gouzoulis-Mayfrank et al., 1998; Gouzoulis-Mayfrank et al., 2005; Heekeren et al., 2007; Hoch, 1951; Hoffer, Osmond, & Smythies, 1954; Vollenweider et al., 1998; Halberstadt & Geyer, 2013; Murray, Paparelli, Morrison, Marconi, & Di Forti, 2013). However, important differences have been demonstrated. For example, in healthy participants, classic psychedelic effects show some similarity to, or model, the positive (e.g., thought disorder, inappropriate affect) but not negative symptoms (e.g., flat affect, lack of motivation) of psychotic disorders (Gouzoulis-Mayfrank et al., 2005; Heekeren et al., 2007). Perhaps more importantly, these drug-occasioned adverse subjective experiences differ from psychotic disorders in that they have a clear cause (i.e., acute drug effects), and they resolve at the resolution of drug effects in the overwhelming majority of psychiatrically screened populations under appropriate safeguards as discussed above (e.g., Cohen, 1960; Johnson et al., 2008). However, such adverse subjective experiences in unscreened and unsupervised individuals appear to precipitate enduring psychotic reactions among some individuals (e.g., 3 among 1993 individuals who endorsed adverse subjective experiences in a survey focused on such experiences; Carbonaro et al., 2016).

Another category of risk involves short-term physiological effects. Classic psychedelics modestly raise blood pressure and heart rate during their acute course of effects (Griffiths et al., 2006; Griffiths et al., 2011; Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004; Isbell, 1959; Strassman & Qualls, 1994; Gouzoulis-Mayfrank et al., 1999; Passie et al., 2002; Wolbach, Isbell, & Miner, 1962; Wolbach, Miner, & Isbell, 1962). Therefore, those with severe cardiac disease should be excluded (Johnson et al., 2008). Adverse events that can be caused by the administration of classic psychedelics, but that do not pose substantial obstacles for their clinical administration to most individuals, are dose-related headaches (Johnson, Sewell, & Griffiths, 2012), relatively low ratings of nausea (Griffiths et al., 2011; Carbonaro, Johnson, Hurwitz, & Griffiths, 2018), and relatively infrequent vomiting (e.g., 2 of 20 participants vomited after receiving a high dose of 30 mg/70 kg psilocybin, although no participants vomited after 10 or 20 mg/70 kg; Carbonaro et al., 2018). A review of the risks of human classic psychedelic administration research and guidelines for minimizing these risks (Johnson et al., 2008), as well as a review of public health harms associated with psilocybin and other classic psychedelics (Johnson, Griffiths, Hendricks, & Henningfield, 2018), are available elsewhere.

1.3. Pre-historical and historical use of classic psychedelics

Classic psychedelic use by humans appears to be ancient (e.g., Akers, Ruiz, Piper, & Ruck, 2011; Bruhn, De Smet, El-Seedi, & Beck, 2002; Carod-Artal & Vázquez-Cabrera, 2006). Among the varied indigenous societies that have used them, classic psychedelics are widely considered sacraments for use in religious and/or healing contexts (Johnson et al., 2008; Schultes, 1969; Schultes, Hofmann, & Rätsch, 2001). Although mescaline was isolated and identified as the main psychoactive compound in peyote around the turn of the century (Heffter, 1898), it was not until after nearly a half century later, when the psychoactive effects of the synthetic compound LSD were discovered using astonishingly low sub-milligram human doses (Hofmann & Ott, 1980), that clinical interest in classic psychedelics began in earnest (Grinspoon & Bakalar, 1979). Classic psychedelics attracted great interest within psychiatry and the emergent fields of molecular neuroscience and the neuroscience of serotonin in the 1950s to 1960s (Grinspoon, 1981). Promising results were reported for both end-of-life psychological distress and addiction, and classic psychedelics served as tools for studying the biological bases of psychological disorders. The most promising indications examined for classic psychedelic treatment were cancer-related psychological distress (Cohen, 1965; Kast, 1967; Kast & Collins, 1964; Kurland, 1985; Kurland, Pahnke, Unger, Savage, & Goodman, 1969; Kurland, Grof, Pahnke, & Goodman, 1973; Pahnke, Kurland, Goodman, & Richards, 1969; Richards, 1979; Richards, Grof, Goodman, & Kurland, 1972; Richards et al., 1979) and addiction (Bowen, Soskin, & Chotlos, 1970; Chwlos, Blewett, Smith, & Hoffer, 1959; Hollister, Shelton, & Krieger, 1969; Kurland, Savage, Pahnke, Grof, & Olsson, 1971; Ludwig, Levine, Stark, & Lazar, 1969; Savage & McCabe, 1973; Tomsovic & Edwards, 1970). Despite promising findings, this earlier era of human research with classic psychedelics came to a stop in the early 1970s because use of the compounds outside of controlled research settings had become popular and associated with the counterculture movement of the time (Stevens, 1987; Nutt, King, & Nichols, 2013). After decades of dormancy, classic psychedelic research re-emerged in the 1990s (e.g., Spitzer et al., 1996; Strassman & Qualls, 1994; Vollenweider et al., 1997).

2. Epidemiology of classic psychedelic use

2.1. Historical background

Several lines of archaeological evidence suggest that humans have used classic psychedelics in sacramental healing contexts since prehistoric times (Guerra-Doce, 2015; Schultes, 1969). For instance, paintings and sculptures depict stylized humanoids with mushroom features (Froese, Guzmn, & Guzmn-Dvalos, 2016), peyote bulbs stored in southwestern Texas caves have been radiocarbon dated to 3780–3660 BC (El-Seedi, De Smet, Beck, Possnert, & Bruhn, 2005), and classic psychedelic alkaloids have been found in both artifacts and human skeletal remains (Guerra-Doce, 2015). It also has been speculated that the ritualistic sacrament soma, mentioned in the ancient Indian Rig-Veda texts, contained psilocybin mushrooms, fly agaric, and/or other psychoactive plants (Levitt, 2011; McKenna, 1993), and the ancient Greek drink

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kykeon, used as a ceremonial rite for millennia in Eleusis, may have contained ergoline alkaloids, including lysergic acid amides (Webster, 2000). Nevertheless, the prevalence of classic psychedelic use prior to the 20th century is unknown.

Scientists investigated the psychoactive effects of the peyote cactus in the late 19th and early 20th centuries, isolating its psychoactive component, mescaline (Bruhn & Holmstedt, 1974; Schultes, 1969). In 1943 Albert Hofmann serendipitously discovered the psychedelic effects of LSD, which was followed by widespread interest in the psychiatric applications of this novel compound (Hofmann et al., 2013; Osmond, 1957). Shortly thereafter in 1955, banker and amateur mycologist R. Gordon Wasson traveled to the Sierra Mazateca of southern Mexico to document the traditional indigenous use of psilocybin mushrooms. The widely circulated American weekly news magazine *Life* published Wasson's experiences in 1957 ("Seeking the Magic Mushroom," 1957), thrusting psilocybin mushrooms into the public eye. Aided by several high profile advocates (e.g., Cary Grant, Ken Kesey, Timothy Leary, and Paul McCartney; Lee & Slain, 1992; Stevens, 1987) classic psychedelics were soon part of both the Western cultural vernacular and the scientific and clinical pharmacopeia.

2.2. Early epidemiological surveys

Among the first epidemiological surveys on classic psychedelic use was *Life Styles and Campus Communities: A Report of a Survey of American Colleges and Universities*, funded by the National Institutes of Mental Health and conducted by Johns Hopkins University. First published in 1972 and later included in the 1974 *Recent Surveys of Nonmedical Drug Use: A Compendium of Abstracts*, this study of 7948 United States college students found that 8.6% reported having ever used a classic psychedelic in 1970 and 12.6% reported having ever used a classic psychedelic in 1971. Of the sample, 1.5% reported "regular use" of classic psychedelics, defined as using at least once every one to two weeks during the academic year (Rossi, Groves, & Grafstein, 1972; Glenn & Richards, 1974).

Drug Experience, Attitudes, and Related Behavior among Adolescents and Adults: Detailed Tabulation, conducted by the Response Analysis Corporation (Response Analysis Corporation, 1973), reported on a national cross-section of 2411 United States adults surveyed in 1972. This report found that 4.6% of all respondents reported having ever used LSD, with men (7.2%) reporting a higher prevalence than women (2.2%). Furthermore, 22% of 18 to 21 year-olds and 18.2% of 18 to 25 year-olds reported having ever used LSD. The Response Analysis Corporation also surveyed 880 United States youth aged 12 to 17. Of these respondents, 4.8% reported having ever used LSD, with girls (5.4%) reporting a slightly higher prevalence than boys (4.4%).

Two additional early surveys included a study of 5050 United States college students (Gergen, Gergen, & Morse, 1972; Glenn & Richards, 1974) and a study of 1517 boys starting tenth grade in public high schools in the fall of 1966 (Johnston, 1973). Of the United States college student respondents, 11.7% reported having ever used LSD or mescaline. Moreover, of the tenth grade boys, 6.8% reported having ever used classic psychedelics in some manner.

In sum, early epidemiological surveys were limited in scope (e.g., consisting of only youth or only college students) and limited in size (880 to 7948 volunteers), but suggest that classic psychedelic use and LSD use in particular was not uncommon among adolescents and young adults in the late 1960s and early 1970s.

2.3. The "Monitoring the Future" survey

Among the first systematic and rigorous epidemiological surveys to assess classic psychedelic use was Monitoring the Future (MTF). Funded by the National Institute on Drug Abuse, MTF has surveyed approximately 50,000 12th graders every year since 1975 and a similar number of 8th graders, 10th graders, college students, and young adults every year since 1991 (Miech et al., 2017).

Fig. 1 displays past 12 months prevalence of LSD use among 8th graders, 10th graders, 12th graders, college students, and young adults from 1975 to 2016 and Fig. 2 presents past 12 months prevalence of "hallucinogens other than LSD" use among these groups across the same time period. Although the aggregated non-LSD hallucinogens include, per MTF methods, the dissociative anesthetic phencyclidine, concentrated tetrahydrocannabinol, and unknown hallucinogens, it also includes the classic psychedelics mescaline, peyote, and psilocybin. According to MTF, the majority of hallucinogens other than LSD use is accounted for by psilocybin. As seen in the Fig. 1, past 12 months prevalence of LSD use peaked in the mid-1990s for all groups before declining and remaining somewhat constant since the early 2000s. As shown in Fig. 2, past 12 months prevalence of hallucinogens other than LSD use was at its highest point among 12th graders in the first year of the MTF survey in 1975, declined until 1992, then increased before reaching another high among all groups in the early 2000s. Past 12 months prevalence of hallucinogens other than LSD use has steadily declined since this time. The prevalence of lifetime use and past 30 days use, also estimated by MTF but not reported here, exhibit similar time trends, though as expected the prevalence of lifetime use is greater and the prevalence of past 30 days use is smaller than the prevalence of past 12 months use. It is noted that in Fig. 2 the uniform spike in prevalence among 8th, 10th, and 12th graders between 2000 and 2001 is likely due a change in methods in which the term "shrooms" was added to the query assessing psilocybin use (Miech et al., 2017).

2.4. National Survey on Drug Use and Health

The National Survey on Drug Use and Health (NSDUH) of the Substance Abuse and Mental Health Services Administration of the United States Department of Health and Human Services (USDHHS) has been conducted since 1979 to estimate the prevalence of substance use and mental illness in the general United States civilian non-institutionalized population (aged 12 and older; Center for Behavioral Health Statistics and Quality, 2016). Initially the NSDUH queried respondents as to how many times they had used a "hallucinogen" (including the dissociative anesthetic phencyclidine) in their lifetime, making it difficult to determine the prevalence of classic psychedelic use. In 1985, the NSDUH began to query respondents with regard to specific substances used, allowing for estimates of the lifetime prevalence of LSD, peyote, mescaline, and psilocybin use. These data are presented in Fig. 3 below.

As seen in this figure, whereas the lifetime prevalence of peyote and mescaline use has remained relatively constant since 1985, the lifetime prevalence of LSD and psilocybin use increased between 1985 and the early 2000s. Whereas the lifetime prevalence of LSD use has slightly decreased since the early 2000s, the lifetime prevalence of psilocybin use has slightly increased since this time. It is noted that differences in time trends between the NSDUH and MTF are likely attributable to the younger demographic captured by MTF.

2.5. Drug Abuse Warning Network

Another important source of information with regard to prevalence of classic psychedelic use is number of emergency department (ED) visits, or "cases," related to these substances. The Drug Abuse Warning Network (DAWN) was established in 1972 by the Drug Enforcement Administration (DEA) to monitor drug-related ED cases. Data pertaining to ED cases associated with classic psychedelic use are available from 2004 to 2011 (Center for Behavioral Health Statistics and Quality, 2012; Center for Behavioral Health Statistics and Quality, 2013). These data are presented in Fig. 4 below. As shown in this figure, ED cases associated with classic psychedelic use rose slightly from 2004 to 2011, increasing by approximately one case over this time. "Miscellaneous hallucinogens" (defined as novel 2C-X compounds, *Datura stramonium*, mescaline, morning glory seeds, psilocybin, *Salvia divinorum*, and "Hallucinogens Not Otherwise Specified") account for the highest

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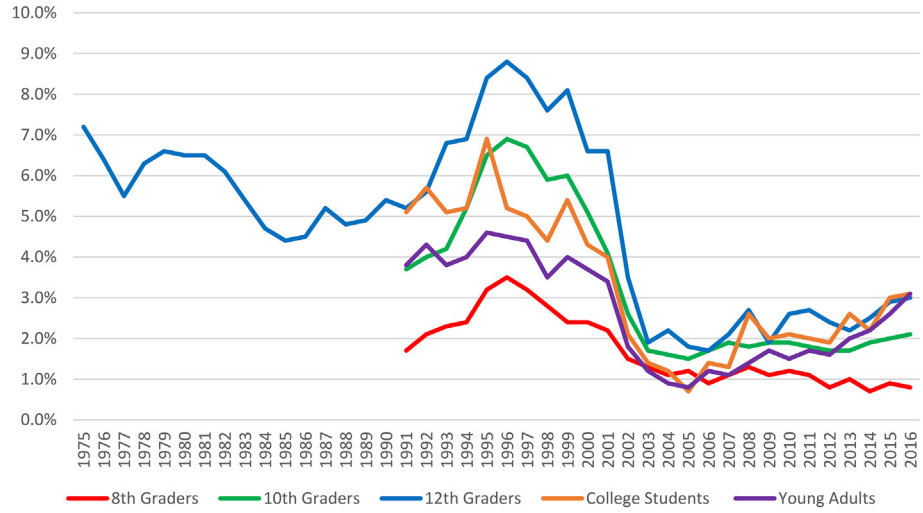

Fig. 1. Past 12 months prevalence of LSD use among United States high school students, college students, and young adults by year from 1975–2016 (Monitoring the Future)

percentage of ED cases among all psychedelic-associated categories, and some of these substances are not considered classic psychedelics (e.g., *Salvia divinorum*). The "Hallucinogens Not Otherwise Specified" category includes 5-MEO-AMT, 5-MEO-DPT, 5-MEO-DMT, AMT, ayahuasca, DMT, LSA, nutmeg, and other purportedly hallucinogenic plants and seeds. Some of these substances also are not considered classic psychedelics. Thus, classic psychedelics appear to account for a very small number of drug-related ED visits. Indeed, to place these findings in context, cocaine was associated an average of 163.8 cases per 100,000 ED visits and opioids were associated with an average of 69.2 cases per 100,000 ED visits over the same seven year period. Of course, these reports may in part reflect the relative prevalence of classic psychedelic use as compared to cocaine and opioid use.

2.6. DEA seizures

The DEA provides drug seizure statistics by year on its website starting in 1986. The DEA reports "hallucinogen" seizures in dosage units, which vary among these compounds. Furthermore, the "hallucinogen" category appears to encompass LSD and psilocybin mushrooms as well as the dissociative anesthetics phencyclidine and ketamine and the empathogen/entactogen MDMA. The DEA drug seizure data are therefore weak indicators of the prevalence of classic psychedelic use, but are nonetheless presented here as they reflect trends in the illicit drug market. Fig. 5 displays DEA hallucinogen doses seized since 1985. As shown in this figure, there has been a decrease in seizures since the early 2000s. In the year 2000, a large LSD manufacturing operation was uncovered by the DEA, which likely explains the spike in seizures that year (DEA Website, 2016; DEA News Release, 2003). The data for 2014 are cited as, "preliminary and subject to updating" although through 2018 they have not changed.

2.7. Epidemiological surveys outside the United States

Although the most comprehensive epidemiological surveys have originated in the United States, a number of surveys outside of the United States inform the global prevalence of classic psychedelic use. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has been pooling data intermittently from European Union countries since 1990. Among young adults aged 15 to 34, national surveys report past 12 months prevalence rates of less than 1% for LSD and psilocybin combined, though respondents from Finland, the United Kingdom, the Netherlands, and the Czech Republic report slightly higher rates of use (1% to 2.3%; European Monitoring Centre for Drugs and Drug Addiction, 2016). England and Wales independently monitor lifetime, past 12 months, and past 30 days prevalence of LSD use.

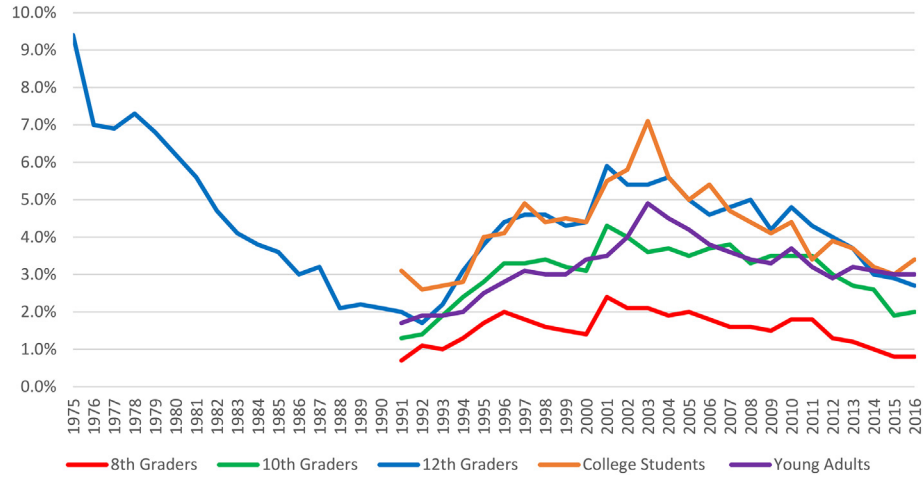

Fig. 2. Past 12 months prevalence of hallucinogens other than LSD use among United States high school students, college students, and young adults by year from 1975–2016 (Monitoring the Future)

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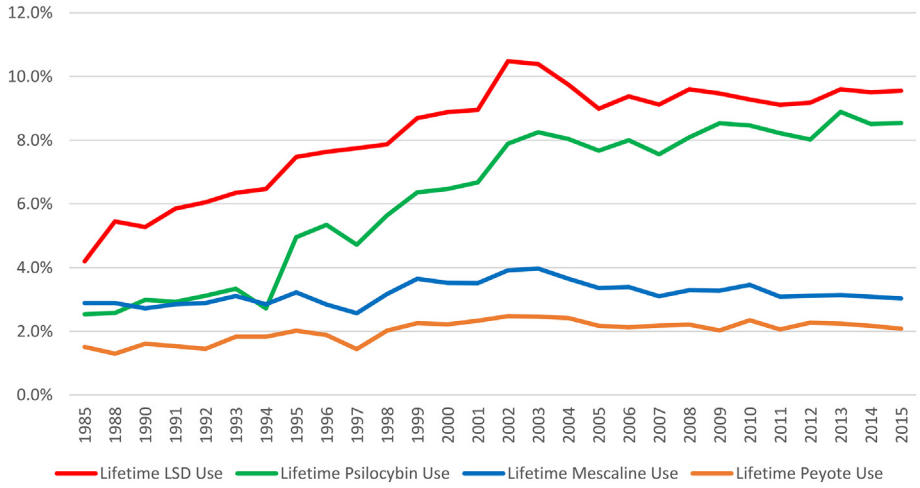

Fig. 3. Weighted lifetime prevalence of LSD, peyote, mescaline, and psilocybin use in the United States population by year from 1985-2015 (National Survey on Drug Use and Health)

Lifetime prevalence rates of LSD use peaked in England and Wales in the late 1990s and early 2000s at approximately 6%. As of 2015, lifetime prevalence of LSD use was 4.4%, past 12 months prevalence of LSD use was 0.2%, and past 30 days prevalence of LSD use approached 0% in England and Wales (European Monitoring Centre for Drugs and Drug Addiction, 2016).

The Global Drug Survey is an online self-selected survey of individuals sampled from the United Kingdom (33.9%), Australia (35.9%), the United States (17.3%), the Eurozone (10%), and Canada (2.9%) initiated in 2012 (Lawn et al., 2014). In total, the Global Drug Survey queried 22,289 individuals, 68.6% of whom were male with an average age of 31.4 years. Fig. 6 summarizes findings from the Global Drug Survey. Of note, 6.2% of Global Drug Survey respondents reported microdosing, or using sub-perceptual doses of classic psychedelics with the intent to improve mood, productivity, and creativity (Linstock et al., 2017). It is noted that because Global Drug Survey participants were self-selected, these statistics are not representative of the general population, and in all likelihood overestimate the prevalence of classic psychedelic use.

The Australian Institute of Health and Welfare has collected data on illicit substance use since 1993. Survey methods are similar to the NSDUH, capturing use prevalence rates of variance substances including "hallucinogens." Though ketamine and MDMA are not included in the hallucinogen category, those substances comprising hallucinogens are not specified. Nevertheless, in 1993 7.3% of respondents (aged 14 and older) reported having ever used a hallucinogen. This figure rose to 9.9% in 1998 and fluctuated around 7% in the early 2000s until peaking again in 2013 at 9.4%. Furthermore, in 1993 1.3% of respondents reported using a hallucinogen in the past 12 months. This peaked in 1998 at 3.0% and then steadily declined to 1.3% in 2013. With regard to frequency of use, 70.2% of respondents who endorsed having ever used a hallucinogen reported using hallucinogens once or twice per year (Australian Institute of Health and Welfare, 2014).

2.8. Special populations

The Native American Church (NAC), Sainto Daime Church, and União do Vegetal (UDV) use classic psychedelic compounds as part of their religious observances in the United States and elsewhere. Prior to the passage of the American Indian Religious Freedom Act (AIRFA) in 1994, which granted the NAC a religious use exemption for peyote, between 1% and 2% of American Indians reported having ever used this substance. Following the passage of the AIRFA, approximately 10% of American Indians reported having ever used peyote. NAC membership is estimated at approximately 600,000 individuals (Prue, 2014). The Santo Daime Church reports that approximately 100,000 people participate in their ayahuasca ceremonies (santodaime.com/en/asks/#28), and the UDV claims over 17,000 members in Brazil in addition to 270 members in the United States (udvusa.org). A number of studies indicate no harm associated with participation in these religious

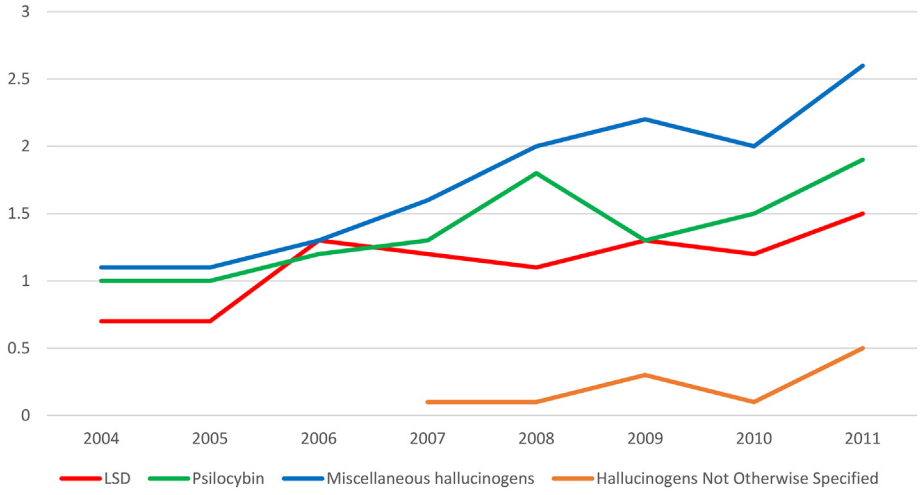

Fig. 4. Classic psychedelic-associated emergency department visits per 100,000 drug-related visits in United States hospitals by year from 2004-2011 (Drug Abuse Warning Network)

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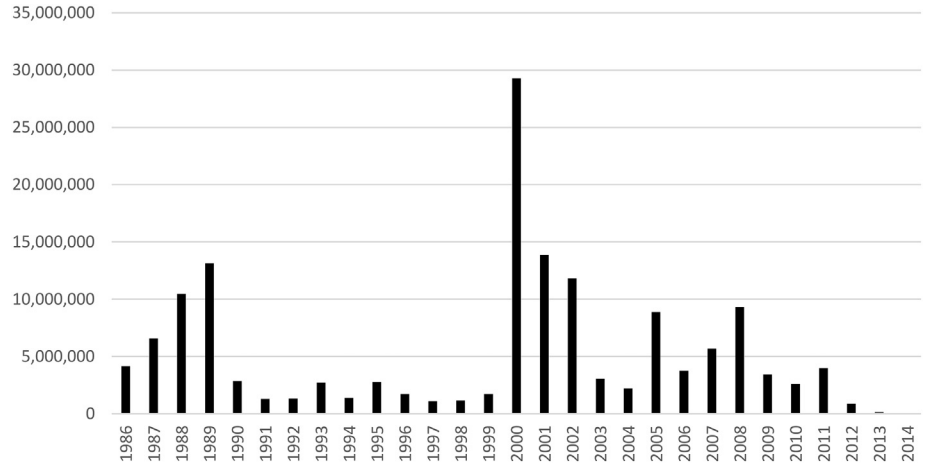

Fig. 5. United States Drug Enforcement Administration hallucinogen dose seizures by year from 1986-2014

observances, and in fact several findings suggest a protective effect with regard to mental health (e.g., Barbosa et al., 2009; Bouso et al., 2012; Doering-Silveira et al., 2005; Fbregas et al., 2010; Halpern et al., 2005, 2008; Miranda et al., 1995).

The United States military has a unique history with LSD, having tested the drug as a potential incapacitating agent, without success, after its discovery by Albert Hofmann in 1943 (Lee and Slain, 1992). Dr. James Ketchum, who was involved in testing LSD at the Army Chemical Center in the 1960s, reported a reduced rate of later death (assessed between 1980 and 1981) among individuals who had previously received LSD (between 1955 and 1975). Specifically, among over 100 individuals who received LSD, only one eventual death was recorded whereas 7.1 were expected to occur (Ketchum, 2006).

2.9. Population-level associations

A number of recent studies have examined population-level associations of classic psychedelic use. Drawing data from multiple years of the NSDUH, Krebs and Johansen (2013) and Johansen and Krebs (2015) found positive trends but no statistically significant associations between lifetime use of classic psychedelics and mental health outcomes, and in fact found some evidence that lifetime use of classic psychedelics was associated with a reduced likelihood of mental health problems. Drawing from a larger number of years of the NSDUH data than the Krebs and Johansen (2013) study but showing similarly sized odds ratios, Hendricks et al. (2015a, 2015b) found that having ever used a classic psychedelic and having ever used psilocybin in particular were both significantly associated with a decreased likelihood of psychological distress and suicidality. Argento et al. (2017) replicated and extended these findings by showing that having ever used a psychedelic, broadly defined (e.g., including MDMA), predicted a decreased likelihood of suicidality among 766 female sex workers in British Columbia. Consistent with recent pilot trials on psilocybin-assisted treatment of addiction (Bogenschutz et al., 2015; Johnson et al., 2014; Johnson et al. 2017), Pisano et al. (2017) found that having ever used a classic psychedelic was associated with a decreased risk of opioid abuse and dependence across multiple NSDUH years. Addressing a line of work that garnered research attention during the first wave of classic psychedelic science (Andersen-Hein, 1963; Leary, 1969; Tenenbaum, 1961), Hendricks et al. (2014) found that naturalistic hallucinogen use predicted a reduced likelihood of supervision failure (i.e., criminal recidivism) among more than 25,000 individuals under community corrections supervision with a history of substance involvement. Walsh et al. (2016) also found that naturalistic hallucinogen use predicted reduced arrest for intimate partner violence among 302 jail inmates, and Hendricks et al. (2018) found that having ever used a

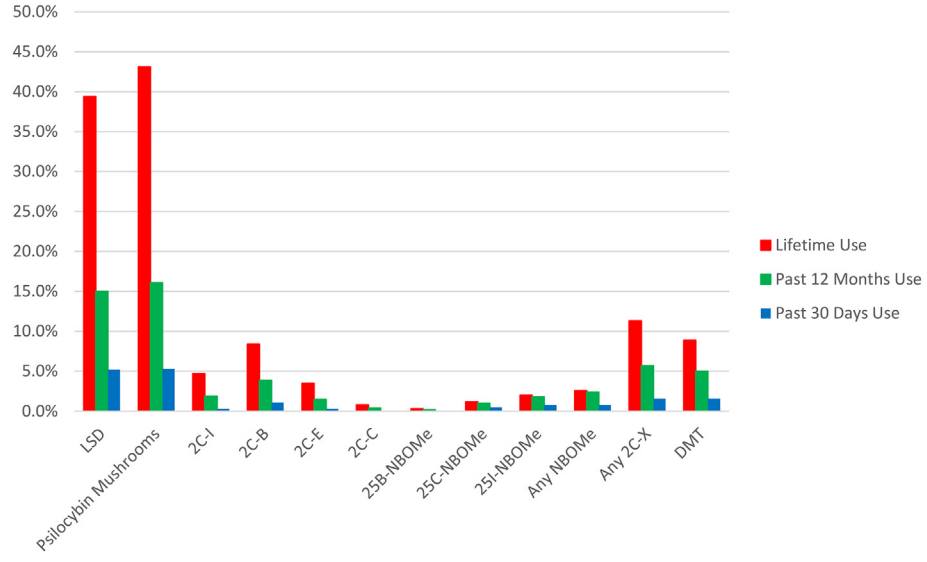

Fig. 6. Self-reported Prevalence of Lifetime Classic and Novel Psychedelic Use, 2013 (Global Drug Survey)

classic psychedelic was associated with a reduced likelihood of larceny/theft and assault using multiple years of NSDUH data. It bears repeating, however, that unsupervised classic psychedelic use can potentially result in dangerous behavior, and prompt or exacerbate psychotic disorders among those predisposed to such disorders (Johnson et al., 2008). Although no contemporary studies have reported psychoses following the administration of a classic psychedelic, rates for developing psychoses following the administration of LSD in studies conducted in the 1960s and 1970s range from .08% to 4.6%, with higher rates among psychiatric patients (Abraham et al., 1996). Clearly then, despite these population-level associations, classic psychedelics are not without risk, and use outside of approved clinical settings is strongly discouraged.

3. Therapeutic effects

Here we review contemporary clinical research examining classic psychedelics in the treatment of cancer-related psychological distress, and the treatment of addictions. One study examined the dose-related effects of psilocybin in the treatment of obsessive-compulsive disorder (Moreno et al., 2006). Although symptoms were reduced temporarily after psilocybin administration, the similar efficacy observed for the high dose and very low dose administered in the study suggests the considerable possibility that results may have been driven by expectancy. Other case-series research has suggested potential efficacy of classic psychedelics in the treatment of cluster headaches, which are notoriously painful and resistant to treatment (Sewell et al., 2006). These patient self-reports suggest that even very low, sub-psychedelic doses of classic psychedelics may effectively abort and prevent cluster headaches. However, because the potential mechanisms at play are likely distinct from the treatment of psychological disorders reviewed herein, this research is not reviewed here. The laboratory clinical trials and pilot studies discussed below have routinely reported the more common adverse events to be expected among classic psychedelic administration studies, specifically, elevated blood pressure and heart rate, psychological discomfort (e.g., anxious or dysphoric reactions), and physical distress (e.g., nausea, vomiting, and headache). While such adverse events are common, they can be managed with appropriate safeguards (Johnson et al., 2008), and do not appear to preclude the possibility of therapeutic benefit.

3.1. Cancer-related psychological distress

All of the studies reviewed in this section and the following *Depression* and *Addiction* sections used a particular treatment approach which was first reported in the scientific literature in 1959 (Chwlos et al., 1959; Majic et al., 2015), and which has come to be known as "psychedelic" psychotherapy. In contrast to the "psycholytic" approach which used lower doses of classic psychedelics, the goal of the psychedelic approach was to administer a high dose in order to occasion a mystical-type experience (sometimes referred to with related terms such as "peak experience" or "ego dissolution") and subsequent behavior change. In addition to the administration of a high dose of a classic psychedelic compound, "psychedelic" psychotherapy includes preparation and rapport building with session facilitators before sessions occur, a comforting physical and interpersonal environment, the use of eyeshades to block visual stimuli, playing carefully selected music during sessions, and follow-up discussion of the session experience.

Following up on the promising findings from trials conducted from the 1950s to 1970s using the psychedelics LSD and dipropyltryptamine (DPT) (Cohen, 1965; Kast, 1967; Kast and Collins, 1964; Kurland, 1985; Kurland et al., 1969; Kurland et al., 1973; Pahnke et al., 1969; Richards, 1979; Richards et al., 1972; Richards et al., 1979), a small pilot study in 2011 compared the effects of a moderate dose of oral psilocybin (0.2 mg/kg) and niacin as a comparator compound within 12 participants with advanced-stage cancer and clinically significant cancer-related anxiety meeting criteria for a DSM-IV anxiety-related disorder (Grob et al., 2011). Importantly, there were no clinically significant adverse events attributable to psilocybin. In a two-week follow-up after drug administration, psilocybin relative to placebo showed a trend toward decreasing depression severity as measured by the Beck Depression Inventory, and anxiety severity as measured by the State-Trait Anxiety Inventory. Relative to scores assessed at study screening, mean depression scores were consistently reduced at each monthly follow-up session, up to the last follow-up at 6 months, when this reduction was statistically significant. Similarly, mean trait anxiety scores were consistently reduced compared to baseline at each monthly follow-up, and this reduction was significant at the 3-month follow-up. This study played an important role in suggesting that the effects reported for LSD and DPT in cancer patients in the earlier era of research are likely relevant to psilocybin as well. Moreover, the study demonstrated safety of psilocybin in this population.

Two larger studies, both using a substantially higher dose of oral psilocybin, were recently published (Griffiths et al., 2016; Ross et al., 2016). One study was conducted in 51 patients with a life-threatening cancer diagnosis who met criteria for at least one DSM-IV mood- or anxiety-related disorder in relation to their cancer (Griffiths et al., 2016). Specifically, these disorders included chronic adjustment disorder with anxiety, chronic adjustment disorder with mixed anxiety and depressed mood, dysthymic disorder, generalized anxiety disorder, and major depressive disorder. Each participant had two drug administration sessions: one in which a high oral dose of psilocybin (22 or 30 mg/70 kg) was administered; and one in which a very low dose of psilocybin (1 or 3 mg/70 kg) was administered as a comparator condition, with the order of the two conditions counterbalanced across participants. Volunteers and session monitors were informed that psilocybin would be administered in both sessions, that the possible dose could range from negligible to high in both sessions, and that at least one session would be at least a moderately-high dose. This instructional set, combined with the use of an inactive or minimally active dose of psilocybin for the comparator condition, maximized expectancy effects for both sessions, thereby increasing the likelihood of positive effects from the low dose and further eliminating the expectancy that an active first session would necessarily be followed by a relatively inactive second session. The high psilocybin dose, compared to the very low dose, significantly improved a variety outcomes measures when measured 5 weeks after each session and before experiencing the other session (if it was still forthcoming). Most astonishingly, results on a number of measures, including the primary clinical outcome measures (Depression: Hamilton Depression Rating Scale, Beck Depression Inventory; Anxiety: Hamilton Anxiety Rating Scale, State-Trait Anxiety Inventory) remained significantly and substantially reduced at the final 6-month follow-up compared to screening scores, with approximately 60% of participants showing scores within the clinically normal range, constituting remission. As discussed in more detail in a later section, ratings of mystical experience occasioned by sessions mediated the effect of psilocybin condition on a number of clinical outcomes. A statistical mediator is a variable that underlies or explains the causal relationship between two other variables. In this case, analysis suggested that the ability of psilocybin to cause positive therapeutic change was due to psilocybin's role in producing mystical-type experience (Baron and Kenny, 1986). No serious adverse effects attributable to psilocybin were observed.

The other study was conducted in 29 patients with a life-threatening cancer diagnosis who met criteria for a DSM-IV anxiety-related disorder in relation to their cancer (Ross et al., 2016). Specifically, these disorders included adjustment disorder and generalized anxiety disorder. Each participant participated in two drug administration sessions. A high oral dose of psilocybin (0.3 mg/kg) was administered in one session, and niacin was administered as a comparator compound in the other. The order of the two conditions was randomized for each participant. Consistent with the results of the larger high-dose study (Griffiths et

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al., 2016), the high dose psilocybin condition produced significant improvements on a variety of outcome measures regardless of order of treatment conditions. At approximately 6 months after treatment, anxiety and depression symptoms remained significantly and substantially reduced compared to screening scores, with an approximately 60% remission rate for key anxiety and depression outcome measures. Ratings of mystical experience were shown to be a mediator of the relation between psilocybin administration and therapeutic effect of psilocybin on anxiety and depression. The different designs used by this study (Ross et al., 2016) and the previously described high-dose psilocybin study (Griffiths et al., 2016) both resulted in surprisingly large and lasting antidepressant and anxiolytic effects, providing complementary support for the efficacy of high-dose psilocybin for cancer-related psychological distress. Like the previous studies, no serious adverse effects attributable to psilocybin were observed.

Another recent study more directly replicated and extended the previous research examining classic psychedelics in the treatment of cancer-related psychological distress by examining the effects of LSD (Gasser et al., 2014). Participants were individuals with anxiety associated with one of several life-threatening diseases. Six of these participants had cancer diagnoses, as did participants in the previously described studies (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Participants received two LSD sessions that were separated by 2 to 3 weeks. Each qualifying participant was randomly assigned to receive either 200 (n = 8) or 20 micrograms (n = 3) of LSD in the context of psychedelic psychotherapy (as in the psilocybin cancer studies), with the same dose delivered in each of the two sessions. The 20 microgram dose was considered an active placebo because it was expected to result in mild, detectable effects but to not generally enhance therapeutic process. At a 2-month follow-up, significant reductions in state anxiety as measured by the State-Trait Anxiety Inventory were observed for the experimental group receiving 200 micrograms of LSD in their sessions, and these approximate levels of improvement were also observed at a 12-month follow-up. In contrast, the active placebo group that received 20 micrograms of LSD in their sessions showed a trend for increased state anxiety at the 2-month follow-up. A similar reduction was observed for trait anxiety in the 200 microgram group, but this did not reach statistical significance. The 20 microgram group showed a trend for increased trait anxiety at the 2-month follow-up. After the 2-month follow-up, participants in the 20 microgram active placebo group underwent a "crossover" to receive the experimental dose of 200 micrograms in two sessions. This resulted in trend decreases in state and trait anxiety 2 months later, and 12-month follow-up anxiety scores similar to those in the experimental group. Like the studies described above examining psilocybin, no serious adverse drug effects were reported.

3.2. Depression

A small open-label pilot study of 12 patients recently examined psilocybin in treatment-resistant major depression (Carhart-Harris et al., 2016a). This study involved two sessions separated by one week. In the first session, patients were orally administered 10 mg of psilocybin. In the second session, 25 mg of psilocybin was orally administered. A number of outcomes, including depression as measured by the Quick Inventory of Depressive Symptoms, and anxiety as measured by the State-Trait Anxiety Inventory, showed statistically significant improvements as compared to screening measures, when assessed both one week and three months after psilocybin treatment. No serious adverse events were attributable to psilocybin administration. A follow-up study reported results for an additional number of participants (for a total N = 20) at 6 months post-treatment. Substantial reductions in depressive symptoms were significant at all time points observed post-treatment, including the 6-month follow-up. Greater ratings of mystical-type experience (measured by factors of unity, spiritual experience, and blissful state on the 11-Dimension Altered States of Consciousness Questionnaire) and ratings of insight for the sessions were significantly related to lower depression scores 5 weeks post-treatment (Carhart-Harris et al., 2018). From this same open-label study, an analysis of 16 patients undergoing fMRI found that increased resting state connectivity within the default mode network (DMN) and between DMN (parahippocampal cortex) and prefrontal cortices observed 1 day after the second of two psilocybin treatments was predictive of clinical response 5 weeks post-treatment (Carhart-Harris et al., 2017). Also from the same open-label study, an analysis of 19 participants undergoing fMRI showed increased amygdala response to emotional faces 1 day after the second of two psilocybin treatments, a finding opposite in direction to previous findings with SSRI treatment of depression (Roseman et al., 2017). These findings suggest potential biological mechanisms for therapeutic efficacy in depression treatment that should be confirmed in randomized controlled treatment trials.

Consistent with the preliminary observations for psilocybin, several studies suggest ayahuasca may hold promise for the treatment of depression. One observational study of 57 non-patient individuals attending ayahuasca ceremonies found significantly decreased ratings of depression and stress (and small, non-significant reductions in anxiety) on the 21-item Depression, Anxiety, and Stress Scale when assessed 1 day and 4 weeks after, compared to before, the ayahuasca ceremonies (Uthaug et al., 2018). Ratings of depression and stress 1 day after the ceremonies were significantly related to the extent of "ego dissolution" in regard to the ayahuasca experiences as rated on the Ego Dissolution Inventory. An open label study of ayahuasca administration (2.2 mL/kg body weight, with 0.8 mg/mL DMT content), was conducted in six patients with recurrent major depressive disorder in an inpatient psychiatric unit (Osório et al., 2015). Ayahuasca administration was followed by statistically significant and substantial reductions in symptom ratings in the Hamilton Depression Rating Scale, the Montgomery-Åsberg Depression Rating Scale, and the Brief Psychiatric Rating Scale anxious-depression subscale at 1, 7, and 21 days post-administration compared to baseline. Using similar methods, the same group replicated these findings in a larger sample of 17 patients with recurrent major depressive disorder (Sanches et al., 2016). Using SPECT imaging, the study also found increased blood perfusion in areas involved in mood regulation (left nucleus accumbens, right insula, and left subgenual area) after ayahuasca administration.

The only randomized controlled trial of a classic psychedelic for treatment-resistant depression examined ayahuasca (Palhano-Fontes et al., 2018). Patients (N = 29 who received intervention) were randomized to receive either ayahuasca (containing 0.36 mg/kg DMT; n = 14) or placebo (n = 15). Although the ayahuasca group showed a trend for higher depressive symptom scores on the Montgomery-Åsberg Depression Rating Scale and the Hamilton Depression Rating Scale before the intervention compared to the placebo group, both scales showed significantly and substantially lower depressive symptoms in the ayahausca group compared to the placebo group 7 days after treatment.

In response to promising results in the treatment of depression with classic psychedelics (both within and outside of cancer contexts), a number of reviews and commentaries have been published. A commonality is acknowledgement of promising findings but recognition of the early stages of this research and the need for larger studies investigating methodological variations, in particular the need for randomized research in non-cancer related treatment-resistant depression, continued research on potential risks, and additional research on potential mechanisms (e.g., dos Santos et al., 2016; Mahapatra and Gupta, 2017; Patra, 2016; Cowen, 2016; McCorvy et al., 2016). A challenge not typically recognized in commentaries is that, despite widespread agreement that systematic and rigorous following is essential, substantial funding is required for large trials and mechanistic studies, and to date, federal funding for such follow-up research has not been provided.

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Hopefully, recent research on depression and other disorders has set the stage for a transition in which public funding for needed follow-up research may be forthcoming (Johnson, in press).

3.3. Addiction

Until recently, reviews of the older literature examining classic psychedelics in the treatment of addictions have concluded mixed results (Abuzzahab and Anderson, 1971; McGlothlin and Arnold, 1971; Halpern, 1996; Mangini, 1998). However, a meta-analysis published in 2012 quantitatively analyzed the effect sizes observed for all six of the studies that randomized alcohol dependent participants to LSD treatment or comparator conditions and found robust support for the efficacy of LSD, showing, for example, that LSD approximately doubled the odds of improved outcomes at the first follow-up (Krebs and Johansen, 2012). In addition to this rigorous quantitative re-analysis of the previous era of research, multiple recent clinical pilot studies have reinitiated interest in the use of classic psychedelics in the treatment of addiction.

One small open-label pilot study of smoking cessation treatment administered psilocybin to 15 treatment-resistant, biologically confirmed smokers, along with cognitive behavioral therapy for tobacco dependence (Johnson et al., 2014). On the target quit date, the timing of which was determined several weeks beforehand, participants were orally administered 20 mg/70 kg psilocybin. Two weeks later, a second oral dose of psilocybin (30 mg/70 kg) was administered. Eight weeks after the target quite date, a third dose (30 mg/70 kg) was administered. The study included the option to administer the 20 mg/70 kg dose during the second and/or third psilocybin sessions dependent on participant response. The treatment program included weekly cognitive behavioral therapy sessions that occurred until 10 weeks after the target quit date (except when a psilocybin session was scheduled). Results showed that 80% of participants were biologically confirmed as abstinent at 6-months post-target quit date, and 60% of participants biologically confirmed as abstinent at 2.5 years post-target quit date (Johnson et al., 2014; Johnson et al., 2017). Although this pilot study contained no comparison group, the abstinence rates were substantially higher than those typically observed in medication and/or behavioral smoking cessation therapies (e.g., typically ≤35% abstinence at 6 months; Johnson et al., 2014). Those participants who had stronger mystical experiences in psilocybin sessions were more likely to be successful in quitting smoking (Garcia-Romeu et al., 2014). Although spirituality is often an aspect of addiction recovery (e.g., Miller, 2004), we are aware of no data to indicate if classic psychedelic-occasioned experiences are identical to those reported in addiction recovery (e.g., 12 step programs) using either validated self-report instruments or at the neurobiological level. No serious adverse events were attributed to psilocybin. A recent survey study examined individuals claiming to have quit or reduced smoking due to a classic psychedelic experience and found that participants typically judged negative affect withdrawal symptoms (e.g., depression, irritability, craving) to be much less severe compared to previous occasions in which they quit smoking (Johnson et al., 2017).

Another small open-label study tested psilocybin in the treatment of addiction, in this case, alcohol dependence (Bogenschutz et al., 2015). Ten participants who met DSM-IV criteria for alcohol dependence participated in up to two oral psilocybin sessions as part of a motivational enhancement therapy program lasting 12 weeks. Upon at least 24 hours of alcohol abstinence, the first psilocybin session occurred, in which 0.3 mg/kg psilocybin was administered. A second dose of 0.4 mg/kg (or 0.3 mg/kg depending on response in first session) was administered four weeks later for a subset of volunteers. Percentage of drinking days and percentage of heavy drinking days significantly decreased following the first psilocybin session. At 36 weeks after treatment, these self-reported drinking indices were still substantially lower than at screening. More specifically, mean percentage of drinking days dropped from approximately 32.5% in the 4 weeks of treatment preceding the psilocybin session, to approximately 12.5% in the 4 weeks following the psilocybin session, and approximately 17.5% at the final follow-up period 21 to 32 weeks after the psilocybin session. Mean percentage of heavy drinking days (i.e., ≥5 drinks for men, ≥4 drinks for women) dropped from approximately 26% in the 4 weeks of treatment preceding the psilocybin session, to approximately 8% in the 4 weeks following the psilocybin session, and approximately 13% at the final follow-up period 21 to 32 weeks after the psilocybin session. A significant relation was found between higher mystical-type experience scores in the first psilocybin session and decreased alcohol use. Importantly, there were no clinically significant adverse events attributable to psilocybin.

4. Mystical experiences

Mystical-type or quantum change experiences are sometimes occasioned by classic psychedelics. Mystical experiences refer to a class of experiences having a primary feature of a sense of the unity of all people and things accompanied by a sense of reverence, and the authoritative truth value of the experience (e.g., Stace, 1960a). Descriptions of spontaneously occurring mystical experiences date back millennia to the early Indian Upanishads and the Greek philosopher Plotinus. Many reports of such experiences have been catalogued and classified by theologians, psychologists, and philosophers (James, 1902; Stace, 1960a,b). Quantum change is a more recently introduced concept that has significant overlap with mystical experience, but in addition to the phenomenology of the experience itself, quantum change emphasizes the persisting consequences caused by the experience. More specifically, quantum change experiences refer to sudden, distinctive, benevolent, and often profoundly meaningful experiences that are said to result in personal transformations that affect a broad range of personal emotions, cognitions, and behaviors (Baka and Miller, 2001; Miller, 2004). The phenomenon of quantum change is differentiated from the usual process of behavioral change, which occurs in small incremental steps (James, 1902). Two subtypes of quantum change experiences have been proposed: the mystical-type (which overlap with classic mystical experiences) and the insightful-type, which emphasize the importance of sudden and compelling personal insight into life problems or circumstances. These overlapping constructs of mystical experience and quantum change experiences have also been variously labeled as conversion experiences, religious experiences, peak experiences, transcendental experiences, transforming moments, or epiphanies (e.g., James, 1902; Stace, 1960; Maslow, 1968; Baka and Miller, 2001). These experiences are scientifically interesting and important to study because they are sometimes associated with abrupt, substantial, and sustained changes in behavior and perception. Furthermore, the authoritative sense of interconnectedness that is a key feature of mystical-type experiences has been proposed by some to be foundational to the world's ethical and moral systems (Huxley, 1947; Stace, 1960a; Jones, 2016). Despite their apparent importance, the unpredictability and low probability of "naturally occurring" mystical-type and insightful-type experiences, whether they occur in religious or nonreligious contexts, has made them inherently difficult to study in controlled empirical research.

Because much more research has focused on mystical experiences than quantum change experiences and relatively little research has assessed insightful-type experiences per se, our emphasis will be primarily on mystical-type experiences. Our summary below draws heavily on a detailed recent review of classic psychedelics and mystical experience (Barrett and Griffiths, 2017).

The most definitive review of mystical experience was compiled by Stace (1960a) who identified and distilled descriptions of mystical experiences from a variety of sources. Stace hypothesized that mystical experiences have a common core of phenomenological features that are independent from the interpretation of those experiences. He proposed that a defining feature of the mystical experience is a sense of unity, or

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the experience of becoming one with all that exists. He distinguished between introvertive (internal) and extrovertive (external) variants of unity experiences. In addition to internal unity and external unity, Stace described several other dimensions of mystical experience: sacredness - a sense that what is encountered is holy or sacred; noetic quality – the experience is imbued with an aspect of meaning and a sense of encountering ultimate reality that is more real than usual everyday reality; positive mood – joy, ecstasy, blessedness, peace, tenderness, gentleness, tranquility, awe; transcendence of time and space – notions of time and space have no meaning during the experience; and ineffability – the experience is difficult to put into words. Stace also cited paradoxicality (the coexistence of mutually exclusive states or concepts) as a dimension of mystical experience, however the validity of that dimension has been questioned in subsequent empirical studies of mystical experience (Hood, 1975; MacLean et al., 2012).

Mystical experiences have been an active area of investigation in the experimental psychology literature, particularly within the psychology of religion (Hood 2009). The Mysticism Scale, a psychometric instrument that codifies the descriptive definition of mystical experience provided by Stace (Hood 1975; Hood et al. 2001) has been used extensively in this research.

4.1. Psilocybin and mystical experiences in healthy volunteers

The long historical use of naturally-occurring classic psychedelics by indigenous populations in ceremonial contexts is well documented (Westermeyer 1988; Wasson et al. 1978; Schultes et al. 2001). Psychoactive plants and fungi for which there is substantive knowledge of ceremonial use include peyote, ayahuasca, and psilocybin mushrooms. The reasons for such ceremonial use included medicinal and divination purposes, but a prominent goal of ceremonial consumption of classic psychedelics has also likely been to occasion mystical-type experiences (Roberts 2001).

The first experimental study to investigate the effects of a classic psychedelic on mystical experience was the so-called Good Friday experiment conducted by Walter Pahnke in 1962. The study involved administration of either 30 mg psilocybin (n = 10) or 200 mg nicotinic acid (n = 10) to seminary students in a private chapel on Good Friday during the broadcast of the traditional Good Friday religious service (Pahnke, 1963). After the experience, and at a 6-month follow-up, participants completed a questionnaire that assessed dimensions of mystical experience that were based on the model of mystical experience developed by Stace (1960a). The mean percentage of maximal possible score for the first 6 Stace dimensions of mystical experience (unity, sacredness, noetic quality, positive mood, transcendence of time and space, and ineffability) was 64.1% among subjects who received psilocybin (Pahnke, 1967b). Pahnke's criteria for a "complete" mystical experience are somewhat unclear, but it appears he considered such experiences as being defined by ratings of at least 60% of the total possible score (Pahnke, 1969) or at least 60% to 70% for each of 9 dimensions (unity, sacredness, positive mood, transcendence of time and space, noetic quality, ineffability, and paradoxicality, transiency, and persisting positive changes in attitudes and behaviors; Pahnke, 1967a). By this criterion, "3 or 4 of the ten psilocybin subjects reached the 60% to 70% level of completeness, whereas none of the control subjects did" (Pahnke, 1967a). In a 25-year follow-up to the Good Friday experiment, Doblin (1991) was able to contact 16 of the 20 original participants and collect additional retrospective ratings. That study found little change between the 6-month retrospective ratings and the 25-year retrospective ratings of mystical experience.

While groundbreaking, the Good Friday experiment had significant limitations, including limited generality due to the highly selective demographics of the participants (seminary students), conduct of the study in a group setting that allowed interactions among participants (thus resulting in nonindependence of individual subject data), explicit instructions to participants that some would and some would not receive psilocybin (thus creating powerful expectancy effects), and the fact that half of the researchers present during the study also received psilocybin. Not surprisingly, under these conditions, the blind was broken shortly after drug administration, which likely contributed to the assessed differences between groups (Doblin 1991; Wulff 1991; Smith 2000).

In a replication and extension of the Good Friday experiment, a double-blind crossover comparative pharmacology study was conducted of psilocybin (30 mg/70 kg) and methylphenidate (40 mg/70 kg) administered in separate sessions to each of 36 participants individually, with at least two months between sessions (Griffiths et al. 2006, 2008). Participants in this study were well educated, psychiatrically and medically healthy, had no prior psychedelic use, and represented a more general sample of the population than those used in the Good Friday experiment. The study reduced expectancy and group confounding effects by studying participants without personal histories of classic psychedelic use, by studying only a single participant at a time, and by using an experimental design and instructions that obscured the range of drug conditions that would be administered as well as the total possible number of sessions. The study also utilized a better control condition (methylphenidate) than the Good Friday experiment (nicotinic acid). Methylphenidate and psilocybin can both induce strong subjective effects with some similarities, and with a reasonably similar time course. Nicotinic acid, in contrast, has a relatively short time course and a profile of subjective effects that is very different from psilocybin. Finally, in addition to using a revised and updated version of the mystical experience questionnaire used in the Good Friday experiment, this study used two psychometrically validated questionnaires that assessed mystical and spiritual effects (the Hood Mysticism Scale and the Spiritual Transcendence Scale) as well as ratings of changes in participants' attitudes and behavior by community observers (family members and friends of participants).

In this and most subsequent studies from the Johns Hopkins laboratory, a 4-scale, 30-item Mystical Experience Questionnaire (MEQ30) was used. The factor structure of the MEQ30 is described in the text box. The MEQ30 is a shortened and psychometrically refined version of the original 43-item Mystical Experience Questionnaire (MEQ43) presented in the appendix to Griffiths et al., 2006. The MEQ30 was validated in both retrospective accounts of mystical experiences with psilocybin (MacLean et al. 2012) and in prospective, experimental laboratory studies with psilocybin (Barrett et al. 2015). The mean percentage of maximum total possible score for the Griffiths et al., 2006 study was 78% and 33% immediately after psilocybin and methylphenidate, respectively, and 76% 14 months after psilocybin (Barrett et al. 2015, appendix 3). Using scoring criteria for having a "complete" mystical experiences that were analogous but more precise than those used in the Good Friday study (i.e. ≥60 percent of the total possible score on each of four factors of the MEQ30), 61% of participants were scored as having had "complete" mystical experiences both at the end of the psilocybin session and at the 14-month follow-up (Barrett et al., 2015, appendix 3). In contrast, 7% of participants met criteria for a "complete" mystical experience at the end of the methylphenidate session. Two months after the session, most participants (71%) rated their psilocybin session as among the top five or single most spiritually significant experience of their lives, compared to 8% of participants after methylphenidate (Griffiths et al., 2006). Ratings of positive attitudes about life and self, positive mood, positive behaviors, and positive social effects 2 months after psilocybin sessions were significantly greater than those provided 2 months after methylphenidate sessions. Further, community observer ratings showed small but significant changes in participants' positive attitudes and behaviors 2 months after the psilocybin sessions, but no changes were found 2 months after methylphenidate sessions. In a 14-month follow-up report, 67% of participants rated their psilocybin session as among the top five most spiritually significant experiences of their lives, and 58% of participants rated their psilocybin session as among the top five most personally meaningful experiences of their

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lives (Griffiths et al. 2008). Ratings of positive behavior, mood, attitude, and social changes associated with the psilocybin session at the 14-month follow-up were not significantly different from those provided 2 months post session. Correlation and regression analyses indicated a central role of mystical experience assessed on the session day, but not intensity of psilocybin experience, in predicting the high ratings of spiritual significance and personal meaning assessed at 14 months (Griffiths et al. 2008).

Four Factors in the Mystical Experience Questionnaire (MEQ30)

Factor 1: Mystical

Internal Unity

Experience of pure being and pure awareness (beyond the world of sense impressions).

External Unity

Experience of oneness or unity with objects and/or persons perceived in your surroundings.

Noetic Quality

Certainty of encounter with ultimate reality (in the sense of being able to "know" and "see" what is really real at some point during your experience.

Sacredness

Sense of being at a spiritual height.

Factor 2: Positive Mood

Experience of amazement.

Factor 3: Transcendence of Time and Space

Loss of your usual sense of time or space.

Factor 4: Ineffability

Sense that the experience cannot be described adequately in words.

The MEQ30 is a psychometrically validated retrospective measure of acute mystical experience (MacLean et al. 2012; Barrett et al. 2015). The four factors of the questionnaire are derived from a total of 30 items that probe seven dimensions (designated by underlines) of mystical experience that were identified by Stace (1960b). The Mystical factor is composed of 15 items probing four dimensions of the Stace model (internal unity, external unity, noetic quality, and sacredness). Positive Mood (6 items), Transcendence of Time and Space (6 items) and Ineffability (3 items) factors correspond to three separate dimensions of the Stace model. The psychometrically validated MEQ30 consists of a subset of items from the older MEQ43. Illustrative items are shown in italics. [Adapted from Barrett and Griffiths (2018)]

An extension of this line of research utilized a double-blind placebo-controlled design that assessed the effects of placebo and a range of psilocybin doses (Griffiths et al., 2011). Eighteen volunteers, with demographics generally similar to those in the previous study, participated. Volunteers received 5, 10, 20, and 30 mg/70 kg of psilocybin in separate sessions with at least one month between each session and a placebo session randomly placed within the sequence. Mystical experience was an increasing function of psilocybin dose (Griffiths et al., 2011; Barrett et al., 2015, appendix 3). The mean percentage of maximum total possible score on the MEQ30 on session days was 23%, 47%, 52%, 70%, and 77% after placebo and 5, 10, 20, and 30 mg/70 kg psilocybin. This score for 30 mg/70 kg at 14 months was 81%. The percentage of participants meeting criteria for a "complete" mystical experience on session days was 6%, 11%, 17%, 61%, and 67%, for placebo and the four doses of psilocybin, respectively. This percentage for 30 mg/70 kg at 14 months was 78%. Ratings 1 month after sessions of the spiritual significance of the experience and positive behavior change attributed to the experience also increased with dose. Eighty-three percent of participants rated the session experiences after 20 and/or 30 mg/70 kg as among the five most spiritually significant experiences of their life; 61% also rated at least one of these as the single most spiritually significant experience of their life. Likewise, 1 month follow-up ratings of positive attitudes about life and self, positive behavior, positive social effects, and increased spirituality generally increased as a function of psilocybin dose. One month follow-up ratings after the 20 or 30 mg/70 kg sessions did not differ from follow-up ratings 14 months after study completion. Finally, compared to pre-study ratings, community observers rated significant positive change in the attitudes and behaviors of participants 3 to 4 weeks after the final session and 14 months after the final session.

A further extension of this research explored the role of psilocybin-occasioned mystical experience in combination with meditation and other spiritual practices to produce enduring changes in trait measures of prosocial attitudes and behaviors (Griffiths et al., 2018). Participants were medically healthy and had relatively low rates of meditation and spiritual practices (e.g., 31% reported some level of current meditation; mean frequency of meditation for all participants was 1.1 times per month). Participants were randomized to one of three groups ($n = 25$ each): 1. very-low-dose (1 mg/70 kg on sessions 1 and 2) with moderate-level ("standard") support for spiritual-practice (LD-SS); 2. high-dose (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with standard support (HD-SS); and 3. high-dose psilocybin (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with high support for spiritual-practice (HD-HS). The standard spiritual support conditions consisted of 7 hours of individual meetings over the study, while the high support condition consisted of 35 hours of individual and group meetings. Meetings consisted of discussion and encouragement for daily meditation, spiritual awareness, and journaling practices. Psilocybin was administered double-blind and instructions to participants/staff minimized expectancy confounds. The proportion of participants who met criteria for having had a "complete" mystical experience on the MEQ30 immediately after sessions 1 and 2, respectively, were 0% and 4% (LD-SS), 48% and 50% (HD-SS), and 44% and 52% (HD-HS). Overall, 4%, 61%, and 64% of participants in the LD-SS, HD-SS, and HD-HS groups had "complete" mystical experiences at either or both sessions 1 and 2. The mean percentage of maximum total possible score on the MEQ30 collapsed across both sessions was 19%, 66%, and 74%, respectively for the LD-SS, HD-SS, and HD-HS groups. At 6 months, compared to LD-SS, both high-dose groups showed large significant positive changes on longitudinal measures of interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, and community-observer ratings. Hierarchical regression analysis was used to examine the relationship of mystical experience (MEQ30 scores) and specific spiritual practices to the various outcome measures that showed between-group differences at 6 months. This analysis indicated that both mystical experience and spiritual practices contribute to positive outcomes, with mystical experience making a substantially greater contribution. The fact that the measure of mystical experience preceded the assessment of outcome measures by 4-5 months strengthens the interpretation that mystical experience and/or its neurophysiological or other correlates are likely determinants of the enduring positive attitudinal, dispositional, and behavioral effects of psilocybin when administered under spiritually supported conditions.

Although the foregoing study of psilocybin combined with spiritual practices showed robust enduring changes in various trait measures suggesting healthy psychological functioning, the study showed equivocal effects on the personality domain of Openness. Specifically, the study showed that Openness increased from screening to 6 months in the HD-HS group but not in the HD-SS or LD-SS groups. However, there were no between-group differences in Openness at 6 months. Further analyses of these data did not show significant relationships between several measures of mystical-type experience and changes in

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Openness. These findings contrast with the results from a previous analysis that showed that psilocybin-occasioned mystical experience was associated with increases in Openness from screening to 1–2 months and to 14 months after psilocybin (MacLean et al., 2011). Increases in Openness have been shown 2 weeks after administration of LSD in healthy individuals (Lebedev et al., 2016). The failure to observe significant increases in Openness in the most recent study might be attributable to engagement in the program of spiritual practices or to some other aspect of the study design.

In a recent study of psilocybin and mystical experience from Johns Hopkins University, Carbonaro et al. (2018) examined single, acute oral doses of psilocybin (10, 20, 30 mg/70 kg), dextromethorphan (DXM; 400 mg/70 kg), and placebo under double-blind conditions to 20 participants with histories of psychedelic use. DXM, an N-methyl-D-aspartate (NMDA) receptor antagonist, was used as a comparator in this study because it is sometimes used at high doses (e.g., ≥300 mg) as an atypical hallucinogen or psychedelic (Banken and Foster, 2008; Morris and Wallach, 2014). Volunteer preparation and session support were similar to previous studies. The mean percentage of maximum total possible score on the MEQ30 at the end of sessions increased with psilocybin dose and was significantly higher after 10, 20, and 30 mg/70 kg psilocybin (39%, 53% and 63%, respectively) than after placebo (8%). Furthermore, the mean percentage of maximum total possible score on the MEQ30 at the end of sessions was significantly higher after 20 and 30 mg/70 kg psilocybin (53% and 63%, respectively) than after DXM (40%). The proportion of volunteers who met a priori criteria for having had a "complete" mystical experience on the MEQ30 was: 0%, 0%, 20%, 40%, and 0% after placebo, 10, 20, and 30 mg/70 kg psilocybin, and DXM, respectively. The incidence of "complete" mystical experience after the 30 mg/70 kg psilocybin dose was significantly greater than after both placebo and DXM.

Barrett and Griffiths (2017) conducted a further analysis of psilocybin-occasioned mystical experience in 119 healthy volunteers by collapsing data at 30 mg/70 kg psilocybin across three studies (Griffiths et al., 2006, 2011, 2018). On the MEQ30 completed on session days, 57% of participants met criteria for a "complete" mystical experience, with the mean percentage of maximum total possible score being 73%. In retrospective follow-up ratings, most participants rated this session experience in the top five most personally meaningful (66%) or spiritually significant (68%) in their lives, with 70% rating moderate or greater positive behavior change that they attributed to the session experience.

4.2. Psilocybin and mystical experiences in therapeutic trials

As previously detailed in Sections 2.1 and 2.3, four studies have assessed psilocybin-occasioned mystical experience in the context of therapeutic trials. All four of these studies showed that psilocybin produced significant increases in mystical experience scores and, consistent with the previous studies showing associations between mystical experience and enduring positive outcomes (Griffiths et al., 2008, 2011), these therapeutic studies suggest similar associations with therapeutic outcomes.

As described in Section 2.1, two studies showed that psilocybin produces substantial and enduring decreases in symptoms of anxiety and depression among patients with a life-threatening cancer diagnosis (Griffiths et al., 2016; Ross et al., 2016). For the Griffiths et al. (2016) study, mean percentage of maximum total possible score on the MEQ30 was significantly higher immediately after the high dose (64%) than after the lower dose (27%). These scores after the first session were significantly correlated with most of the enduring changes in therapeutic outcome measures 5 weeks later. For most measures, this relationship continued to be significant when the intensity of overall psilocybin effect was controlled for in a partial correlation analysis, suggesting that mystical-type experience per se has an important role apart from overall intensity of drug effect. Furthermore, analysis suggested that mystical-type experience was a mediator in positive therapeutic response. Similar to these results, the Ross et al. (2016) study found that the mean percentage of maximum possible total score on the MEQ30 was higher immediately after psilocybin than after niacin (estimated from figures as approximately 66% and 10%, respectively), and correlation analysis controlling for intensity of drug effect and a mediation analysis suggested that mystical experience was a mediator of the therapeutic effects.

As described in Section 2.3, two open-label pilot studies of psilocybin in the treatment of substance dependence have reported data consistent with these findings. In the smoking cessation study (Johnson et al., 2014), mystical experience was assessed with the MEQ43. Nine of 15 participants (60%) had a "complete" mystical experience during one or more of her/his multiple psilocybin sessions (Garcia-Romeu et al., 2014). In 10 of the 13 (77%) sessions in which a "complete" mystical experience occured, it occurred during a high dose (30 mg/70 kg) rather than a moderate dose (20 mg/70 kg) session. Across all psilocybin sessions the mean percentage of maximum total possible score on the MEQ43 was 63%. Significant correlations between mean MEQ43 total scores and smoking craving change scores ($r = -.65$) and urine cotinine ($r = -.56$) were found at the 6-month follow-up. Finally, those participants who showed stronger mystical experiences on psilocybin session were more likely to be successful in quitting smoking (Garcia-Romeu et al., 2014). In the pilot study of alcohol dependence (Bogenschutz et al., 2015), the mean percentage of maximum total possible score on the MEQ43 was 47% ($n = 10$) and 39% ($n = 6$) on session 1 (21 mg/70 kg) and 2 (28 mg/70 kg) respectively. Positive change in drinking was significantly correlated with MEQ43 as well as with other measures of intensity of psilocybin effect.

4.3. Lysergic acid diethylamide (LSD) and mystical experiences

The effects of LSD on mystical experience are of particular interest, as LSD is another classic serotonergically mediated psychedelic. Liechti et al. (2017) present results on the effects of LSD in two studies: 1. a double-blind cross-over study in 16 healthy volunteers comparing placebo and 200 micrograms of LSD; and 2. a double-blind cross-over study in 12 anxious patients with life-threatening diseases comparing 200 micrograms of LSD to a low, placebo-like LSD dose (20 micrograms; Gasser et al., 2014). Estimated mean percentage of maximum total possible score on the MEQ30 was 61% and 2% for LSD and placebo respectively in the healthy volunteers, and 50% and < 5% for 200 micrograms of LSD and 20 micrograms of LSD respectively in the patients. The percentage of participants meeting criteria for a "complete" mystical experience after 200 micrograms of LSD was 12.5% in the healthy volunteers and 17% in the patients. Whether this seemingly lower rate of mystical experience after LSD than psilocybin reflects pharmacodynamic differences between these drugs, the use of a relatively lower dose of LSD than psilocybin, and/or differences between the studies in set, setting, or participant characteristics is unknown. Future research should directly compare LSD and psilocybin within subjects, ideally using procedures to minimize expectancy effects.

5. Brain network changes as mechanisms underlying classic psychedelic effects

The brain is composed of many levels of embedded complex systems. These systems have modularity, in the sense that individual nodes or brain regions that subserve certain individual functions (such as representing line orientation, brightness, and hue of a visual stimulus) are segregated from nodes that serve other functions (such as nodes that represent sounds or bodily sensations, or nodes that represent tactile sensation or motor movement). The embedded complex systems of the brain also require integration (i.e.,connection and communication) between nodes in order to support efficient communication between modules that underlie complex processes (such as hand-eye coordination). A balance of modularity

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and efficient integration is necessary to support normal waking consciousness.

Resting-state fMRI connectivity analyses have shown that, under normal conditions, communication between areas of the brain is organized into stable networks (Yeo et al., 2011; Power et al., 2011; Doucet et al., 2011) that demonstrate both modularity and integration (Sporns, 2011). Commonly identified networks underlie sensory, motor, and cognitive processes (Smith et al., 2009, Shirer et al., 2012) and have features that are unique between individuals and stable enough within-individuals that separate scans from the same individual can be identified with very high accuracy (99% or greater) in a large database of scans ("connectome fingerprinting"; Finn et al., 2015; Airan et al., 2016). In such fingerprinting analyses, connectivity among higher-order brain regions involved in self-referential processing and attention show the greatest inter-individual differences and typically contribute most to identifying an individual's connectivity pattern within a large database of connectivity patterns (Finn et al., 2015; Airan et al., 2016). Individual differences in the connectivity of these networks may in a sense constitute an individual's "neural identity."

While typically observed brain networks are reliably found under normal circumstances in resting-state functional connectivity data, activity and correlation within (modularity) and between (integration) these networks has been shown to decrease during the acute effects of psilocybin (Carhart-Harris et al., 2012a; Muthukumaraswamy et al., 2013), ayahuasca (Palhano-Fontes et al., 2015), and LSD (Carhart-Harris et al., 2016b, Speth et al., 2016). In particular, activity and connectivity of brain regions crucial to self-referential processing (including regions of the DMN such as the posterior cingulate cortex) are most strongly impacted by classic psychedelics (Carhart-Harris et al., 2012a, 2016b; Palhano-Fontes et al., 2015). Decoupling and decreased modularity of typically observed large-scale/long-range brain networks has been shown (Lebedev et al., 2015), and during acute drug effects, the brain reorganizes into new, local range networks (Petri et al., 2014). An increased number of distinct patterns in the brain compared to normal waking consciousness has been demonstrated with both psilocybin (Tagliazucchi et al., 2014) and LSD (Schartner et al., 2017), and the overall connectivity and global integration of the brain was shown to increase in a manner that was correlated with subjective reports of "ego dissolution" during LSD[1] (Tagliazucchi et al., 2016). Changes in the brain during the acute effects of classic psychedelics have more generally been associated with subjective effects including "dissolution of the self or ego" (Carhart-Harris et al., 2014) and mystical-type (Barrett and Griffiths, 2017) or spiritual (Kometer et al., 2015) experiences that may have therapeutic value (Garcia-Romeu et al., 2014; Griffiths et al., 2016; Ross et al., 2016; Barrett and Griffiths, 2017).

Overall, the acute effects of classic psychedelics on measures of systems-level neural functioning have included a decrease in both modularity and integration of commonly identified brain networks, and a reconfiguration of communication in the brain. Increased brain entropy[2], which is a physical measure of increased randomness or uncertainty within a system, has been proposed as a mechanism of acute altered states of consciousness with psilocybin (Carhart-Harris et al., 2014) and LSD (Lebedev et al., 2016; Schartner et al., 2017). While this large-scale principle may be at work in the brain during an experience with a classic psychedelic, it does not explain the formation of new, local networks in the brain (Petri et al., 2014) or the observed increases in the number of distinct patterns in the brain compared to normal waking consciousness (Tagliazucchi et al., 2014). An account of temporary and structured reconfiguration of the brain, rather than only increased randomness in the system (entropy), is more consistent with reported data.

Electro- and magneto-cortical studies have demonstrated a broadband reduction of oscillatory power (i.e., decreased brainwave amplitude), and especially low-frequency oscillations (alpha band), by psilocybin (Kometer et al., 2013, 2015, Muthukumaraswamy et al., 2013) and ayahuasca (Riba et al., 2002, 2004, Valle et al., 2016). While oscillations in the same frequency band can serve different functions in different regions of the brain (e.g., theta band oscillations in the hippocampus may not serve the same function as theta band oscillations in the thalamus), lower-frequency oscillations are generally known to modulate information in higher frequencies (Buzsaki et al., 2013). In particular, alpha band synchrony modulates attention and information selection processes that are subserved in higher frequency bands (e.g., gamma; Klimesch, 2012), and serves a specific role in modulating top-down cortical control, which allows for maintenance of integration and modularity of brain networks through altering the transient coupling between and among networks of brain areas (Bazanova and Vernon, 2014). Synchronization of alpha oscillations between parahippocampus, retrosplenial (near posterior cingulate cortex or PCC), and lateral orbitofrontal cortices (regions associated with the DMN) is associated with psilocybin-induced spiritual experience (Kometer et al., 2015), and decreases in alpha power in the PCC are associated with psilocybin-induced "disintegration of the self or ego" (Carhart-Harris et al., 2014). Thus, decreased alpha synchrony in the brain may be an electrocortical mechanism resulting in decreased integration and modularity of typically observed brain networks, and may be critical to the formation of temporary, new, local and stable networks (Petri et al., 2014) and distinct patterns of activity (Tagliazucchi et al., 2014) that are observed during acute classic psychedelic drug effects.

While fMRI, EEG, and MEG measures have primarily shown classic psychedelics to produce an overall reduction in activity and connectivity in the brain, early molecular imaging studies, including PET and SPECT demonstrated various signs of increased brain activity during acute effects of psilocybin (Vollenweider et al., 1997, 1999, Gouzoulis-Mayfrank et al., 1999) and mescaline (Hermle et al., 1992). Along with reports of decreased measures of metabolic activity in subcortical (e.g., thalamus) and posterior (e.g., parietal, occipital, temporal) regions, these molecular imaging studies found a relative increase in activity of frontal brain regions in particular to be a prominent acute neural effect of classic psychedelic drugs. Evidence suggesting a resolution of this discrepancy in the literature was recently provided (Lewis et al., 2017), showing that an overall decrease in brain activity is found when assessing the effects of classic psychedelics on global or absolute cerebral blood flow, and findings of hyperfrontality are recovered when calculating relative cerebral blood flow, which controls for global changes in blood flow. The implication of this finding is that, while overall blood flow may decrease in the brain during the effects of classic psychedelics, these blood flow decreases are not as substantial in prefrontal brain regions in that some frontal regions may be partially spared in relation to posterior brain regions. However, it has yet to be determined whether these relative differences in activity observed in early PET studies relate to increases or decreases in modularity or integration of brain networks. Also, it is as yet unclear whether overall decreases in blood flow, or the relative balance of frontal activity relative to activity in other brain regions, is more directly responsible for the acute effects of classic psychedelics. It is likely that both processes contribute to the unique character of experiences occasioned by the administration of classic psychedelics.

[1] These reports were collected by asking volunteers to respond to questionnaire items such as "I experienced a dissolving of my self or ego" though it is not clear that any further definition was given to volunteers for the terms "self" or "ego."

[2] Entropy as utilized by Carhart-Harris et al. (2014) was formally calculated as the Shannon entropy of intra-brain-network synchrony – more specifically, the negative logarithm of the probability distribution of the variance in the synchrony between nine canonical brain networks. To the degree that only a single event within a probability distribution of a function occurs with high probability, the probability distribution will not be flat, and the frequency of events generated from that distribution will be far less random (or far more predictable) than a probability distribution in which all events occur with equal probability and from which any given event will be nearly unpredictable (or generated from a stochastic process). The former case is a case with very low entropy, and the latter case is a case with very high entropy. Thus, entropy can be used as a formal measure of the randomness or uncertainty within a system.

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5.1. Relation of neural effects to therapeutic effects

The DMN consists primarily of the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and lateral parietal cortex (LPC). The PCC is involved with internally-directed cognition (Leech and Sharp, 2014), the MPFC (and adjacent region of the subgenual anterior cingulate, or sgACC) is implicated in rumination (Cooney et al., 2010; Berman et al., 2011; Kucyi et al., 2014), autobiographical memory recall (Svoboda et al., 2006), self-related judgements and theory of mind processes (Gilbert et al., 2006; Denny et al., 2012), and the LPC has been implicated in a number of processes, including empathy (Kubit and Jack, 2013) and coding a sense of self in spatial cognition (Amorapanth et al., 2010). Impaired connectivity of DMN brain regions to non-DMN brain regions in major depression is associated with greater disorder severity (Seminowicz et al., 2004), and abnormally high connectivity among regions of the DMN and abnormally low connectivity between DMN and executive networks have been implicated in the pathophysiology of major depression (Leibenluft and Pine, 2013). Lower connectivity within the DMN, greater connectivity of sgACC to DMN regions, greater connectivity of sgACC to executive network regions, and greater connectivity within the executive network predict better medication treatment response (Dichter et al., 2015). Neuropathological, molecular imaging, and targeted brain stimulation treatment studies demonstrate that dysregulation of an extended network of brain regions in major depression may originate in abnormalities in medial frontal regions of the DMN (Price and Drevets, 2012). DMN connectivity is normalized along with depressive symptoms after transcranial magnetic stimulation (TMS) of the dorsolateral prefrontal cortex, deep brain stimulation of the subgenual anterior cingulate (Mayberg et al., 2005; Lozano et al., 2012), and electroconvulsive therapy (Cano et al., 2016). This demonstrates a functional relationship between DMN and frontal cortex function and depression. It may be that acute reconfiguration of brain networks during the effects of classic psychedelics, which strongly impact DMN and frontal brain activity and connectivity, lead to lasting alterations in these networks that represent a systems-level mechanism by which classic psychedelics may have efficacy in treating depression. However, the enduring effects of classic psychedelics on the brain have not yet been demonstrated.

A growing body of evidence suggests that traditional antidepressants, as well as novel medications effective in treatment-resistant depression, exert their therapeutic efficacy via the indirect, downstream action of glutamate (Cryan and O'Leary, 2010; Deutschenbaur et al., 2016; Duman et al., 2012; Duman and Voleti, 2012; Dutta et al., 2015; Sanacora et al., 2008; Skolnick et al., 2009, Krystal et al., 2013). Depressed patients have lower glutamate/glutamine levels at baseline (Hasler and Northoff, 2011) and reduced baseline glutamate levels are positively correlated with subsequent antidepressant response to ketamine (Salvadore et al., 2012). Biophysical computational models have implicated specific dysfunction of the glutamatergic activity in medial frontal regions of the DMN as the mechanism that underlies impairments in functional connectivity of this region in major depressive disorder (Ramirez-Mahaluf et al., 2017). Recent magnetic resonance spectroscopy (MRS) studies demonstrate that psilocybin decreased blood oxygenation level dependent (BOLD) activity and increased glutamate concentration in healthy individuals in the anterior cingulate cortex (ACC; Preller et al., 2016), in a manner consistent with therapeutic response in the ACC in patients who are being treated for depression. Thus, a molecular mechanism of action of classic psychedelics may be to alter the connectivity and activity of brain regions implicated in the pathophysiology of depression by altering glutamatergic functioning in these regions (Vollenweider and Kometer, 2010).

If a hyperactive and hyperconnected DMN underlies depression, a hypoactive and hypoconnected DMN may underlie addiction. The cycle of addiction is now understood to relate to a disruption of the balance between reward and limbic brain circuitry and top-down cortical control (including control from prefrontal/executive networks and the DMN) (Volkow et al., 2016). DMN and prefrontal/executive network connectivity is decreased in chronic cocaine (Gu et al., 2010), nicotine (Cole et al., 2010), and heroin (Jiang et al., 2011) users. The typically observed balance between activity and connectivity of DMN and prefrontal/executive networks is also altered during craving in volunteers with substance use disorders (Lerman et al., 2014, Sutherland et al., 2012, Lu et al., 2014). Reduction of craving and withdrawal symptoms may result from normalization of these abnormal connectivity patterns (Cole et al., 2010). Similar to depression, acute and/or lasting reconfiguration of brain networks, in particular prefrontal and DMN regions, by classic psychedelics may represent systems-level mechanisms supporting therapeutic effects of classic psychedelics.

5.2. Insights into the biological basis of consciousness

Neurobiological studies of the effects of classic psychedelics have yielded insights that may be relevant to understanding the biological basis of consciousness. It is notable that conscious awareness can be maintained during classic-psychedelic experiences (i.e., experiences resulting from the administration of a classic psychedelic), yet this conscious awareness appears to be vastly different than normal waking consciousness. During classic-psychedelic experiences, the underlying functional connectivity of the brain is also vastly altered. This suggests that there may be a relationship between the changes in functional brain connectivity during classic-psychedelic experiences and the changes in consciousness that are encountered during classic-psychedelic experiences. Communication within and between networks of brain regions may constitute a biological carrier signal on which awareness and a sense of self emerges, but conscious awareness need not be constrained by the typical patterns of communication between and within brain networks. Thus, not only does the brain show plasticity, but we are learning clearly that discrete interventions that vastly alter brain communication can be achieved with classic psychedelics, and these alterations may be the neurobiological basis of quantum change sometimes observed behaviorally after the administration of classic psychedelics.

6. Conclusions

Contemporary therapeutic research with classic psychedelics has shown promising effects for both cancer-related psychological distress, and addiction to both tobacco and alcohol. In addition, basic scientific studies using classic psychedelics have led to numerous advances in the experimental study of mystical experiences and the study of classic psychedelic mechanisms of action. Perhaps most importantly, neurobiological studies of the effects of classic psychedelics have yielded insights into the biological basis of consciousness. Specifically, these studies collectively suggest the possibility that the pattern and structure of communication between brain networks constitutes the neurobiological basis of consciousness, such that alterations of consciousness are driven by alterations of communication between brain regions. Interestingly, large-scale epidemiological studies of naturalistic classic psychedelic use are consistent with contemporary clinical research, and point to intriguing future trends, namely the application of classic psychedelics in forensic settings.

Promising recent results have been published for cancer-related psychological distress, using both psilocybin and LSD, replicating one major focus of the earlier era of classic psychedelic research. Many of these studies have shown such findings using rigorous double-blind procedures that vary in methods. Consistent signals of efficacy in the face of such variations suggest a robust clinical response. In the United States, if future phase 3 research supports these preliminary findings showing the safety and efficacy of psilocybin in the treatment of cancer-related psychological distress, non-research therapeutic use of psilocybin, under appropriately restricted safeguards adhering to strict

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safety standards (Johnson et al., 2008), may eventually warrant regulatory approval. Additionally, pilot research on treatment-resistant depression also shows preliminary promise in response to classic psychedelic treatment outside of the context of cancer. If such findings are demonstrated in randomized studies, classic psychedelics may be poised as breakthrough medications for the leading cause of worldwide disability, affecting over 300 million human beings (World Health Organization, 2017). Although the clinical research agenda on addictions is at a lesser stage of development in comparison to cancer-related psychological distress, with only open-label pilot studies having been completed thus far in contemporary research (Bogenschutz et al., 2015; Johnson et al., 2014), if randomized clinical trials continue to suggest safety and efficacy, clinical approval of the use of psilocybin for the treatment of specific addiction may also be on the horizon.

If safety and efficacy are sufficiently demonstrated to warrant approved therapeutic use of one classic psychedelic (e.g., psilocybin, LSD), this would suggest the potential therapeutic potential of additional compounds of the same class. In the typical clinical development of other drug classes (e.g., benzodiazepines), a seminal compound of the class is identified and developed for therapeutic use (e.g., chlordiazepoxide), followed by the discovery and therapeutic development of additional compounds of the class over the subsequent decades. However, the clinical development of classic psychedelics may be unique, in that hundreds of psychoactive compounds related to this class have already been identified (e.g., Shulgin and Shulgin, 1991; Shulgin and Shulgin, 1997). Therefore, the broad array of classic and novel psychedelic compounds that have been universally ignored in pharmaceutical drug development may soon constitute a library of potential therapeutics. They may also help to inform the biological mechanisms of human consciousness.

Conflict of interest statement

Roland R. Griffiths is on the Board of Directors of the Heffter Research Institute. The authors declare that there are no other conflicts of interest.

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SB0709 Johnson.pdf
Uploaded by: Matthew Johnson
Position: FAV

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JOHNS HOPKINS
MEDICINE
SCHOOL OF MEDICINE

March 1, 2022

Re: SB0709

Maryland Senate Budget and Taxation Committee

Dear Senators,

I wish to provide testimony regarding SB0709, which involves supporting veterans by funding treatment and treatment research for Post Traumatic Stress Disorder (PTSD), in part regarding psychedelic drugs. I write in support as an individual rather than a representative of Johns Hopkins.

I am the Susan Hill Ward Professor of Psychedelics and Consciousness at Johns Hopkins University School of Medicine and have been conducting research with psychedelics for approximately 18 years. I am regarded as one of the world's leading experts on the efficacy and safety of psychedelics as treatments. I have published seminal work on the risks associated with psychedelics and how they are appropriately addressed in medical practice and research. I have conducted and published studies of psilocybin (the active agent in "magic mushrooms") in the treatment of cancer-related end-of-life anxiety, Major Depressive Disorder, and tobacco addiction.

I wish to make three points:

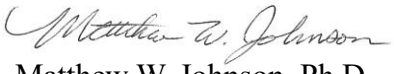
1) Several studies, including ones I have published, over the last decade have shown that psilocybin, in only one, two, or three medication-administration sessions, can cause extremely large reductions in depression, anxiety, and addictive substance use that last for 6 months and even up to several years, and in most patients treated. In the coming months I will be starting a clinical trial testing psilocybin for PTSD, and a study of the alternative treatment "holotropic breathwork" for PTSD. Similar research has found the psychedelic compound MDMA to cause long-standing reductions in PTSD symptoms with only three MDMA administration sessions. Although still going through trials for potential FDA approval for medical use, the results have been extraordinary and constitute, in my opinion, the most significant advances in the treatment of mental health of the last half century. Both psilocybin and MDMA have been officially granted the coveted "breakthrough therapy" designation by the FDA, signifying remarkable promise for a large public health need.

2) There are risks associated with the various psychedelic compounds but these risks are well characterized and methods for squarely mitigating these risks to an acceptable level are well known. This includes patient screening (to exclude for vulnerabilities such as schizophrenia or severe heart disease), preparation for the session including rapport building with the therapists to be with the patient during the psychedelic session, careful monitoring of the psychedelic session by therapists, and follow-up sessions to process the psychedelic experience and probe for any adverse effects.

3) A major obstacles to advancing this research is insufficient funding. The studies discussed above were all supported by philanthropy. Until very recently, the federal government (including NIH) had not funded a therapeutic study with a classic psychedelic compound such as psilocybin for approximately 50 years. The major obstacle to more rapid advancement of this science is insufficient funding for clinical research.

Maryland has long been a national leader in medicine and healthcare. It also happens to be home of some of the earliest promising therapeutic research with psychedelics in the 1960 and 1970s (at the Spring Grove Hospital and the Maryland Psychiatric Research Center). More recently, my research group at Johns Hopkins has been the preeminent research group in the nation during the modern resurrection of psychedelic research. I support SB0709 to maintain Maryland's leading role in medicine and health care, including the therapeutics of psychedelics, by supporting critical research on alternative treatments for veterans with PTSD.

Sincerely,



Matthew W. Johnson, Ph.D.

2022 Beckman Testimony SB0709.pdf
Uploaded by: Robert Beckman
Position: FAV

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TREATNOW TALKING POINTS
Testimony on SB0709, SEN Elfreth
Wednesday, March 2, 2022 - 1:00 PM

PROBLEM:

- Our country's veterans are in a health crisis: the veteran suicide rate is increasing. More veterans and service members are suffering from traumatic brain injuries (TBI) and post-traumatic stress disorder (PTSD). The VA/DoD calls it a suicide epidemic.
- Even though our government is spending billions of dollars on care for TBI and PTSD, it is not stopping the wave of suicides and opioid overdoses, which have continued to increase for more than 15 years. Service member suicides and prescribed drug overdoses total over 200,000 victims since 2003.
- The current standard of care for TBI and PTSD includes prescription drugs that warn of suicidal ideation and talk and cognitive therapy, which only manage symptoms and do not address ***brain wound healing***. Continuing to NOT treat brain wounds will cost taxpayers **$4.7 trillion** over forty years.
- Veterans are not even told that safe, effective, drug-free and non-invasive treatments exist. They are denied INFORMED CONSENT but given drugs that warn of suicidal ideation.
-

SOLUTION:

- Expanding military and VA health care coverage to encompass non-traditional treatment options such as Hyperbaric Oxygen Therapy (HBOT) will save taxpayers $100 billion a year.
- The therapy manipulates oxygen pressure levels for patients over the course of several treatments, ranging from weeks to several months, and is not covered under military health care plans.
- Worldwide clinical studies prove the safety and efficacy of HBOT used to treat TBI and PTSD. The FDA already approves HBOT for fourteen indications, four of which are very similar to brain wounds.

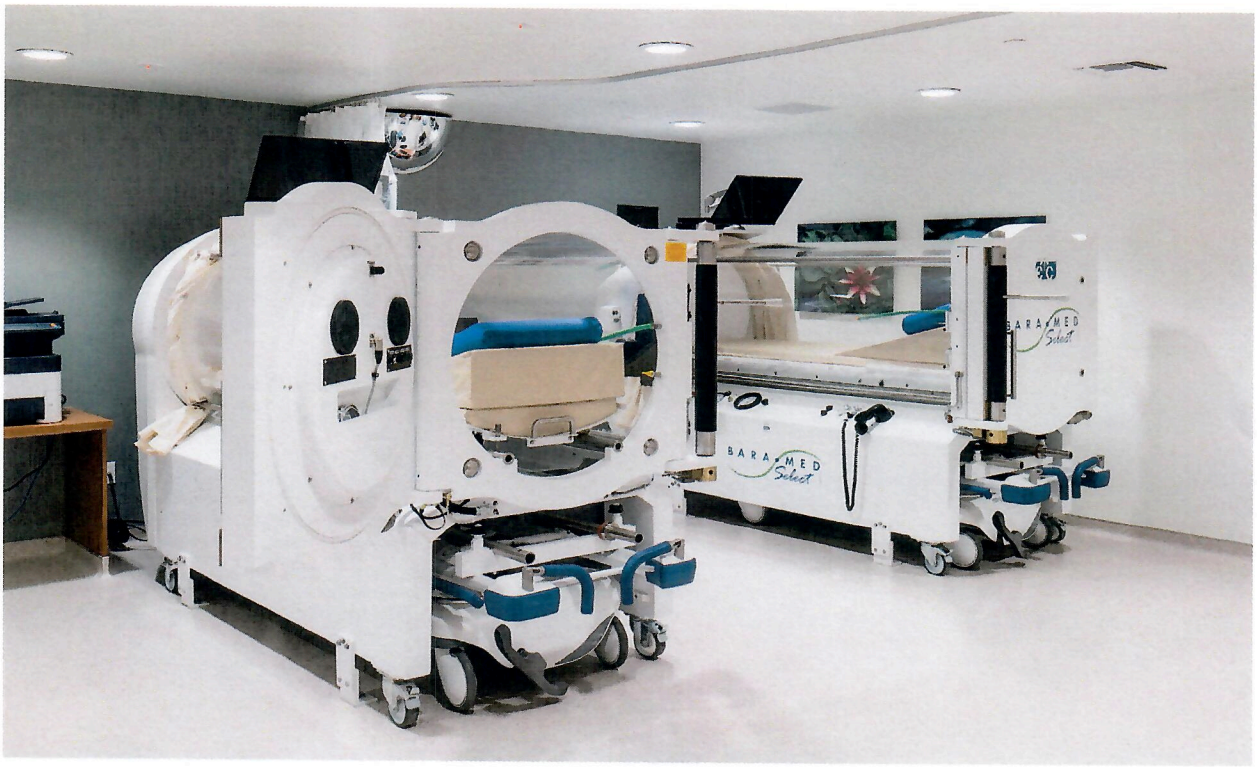
ACTION:

- Eight other states have already enacted legislation calling for the use of HBOT for TBI and PTSD: OK, TX, IN, KY, AZ, FL, NC, WY. Four have allocated up to one million dollars to treat their veterans suffering brain wounds. AZ is contemplating a $3.6M commitment. Other states in the drafting process include CO, MI, OH, and VA.
- At the national level, Bills are being considered and hold the VA accountable to provide Informed Consent and DO NO HARM. Medical Ethics demand that the US government provide ALL the care that is available.

2022 DFU Cost Benefit Analysis 1-6-22.pdf
Uploaded by: Robert Beckman
Position: FAV

Our Veterans Have Earned Easy Access to Diabetic Limb-Saving Care:

Cost Benefit Analysis of Hyperbaric Oxygen Therapy for Veteran Diabetic Foot Ulcers (DFUs) in the VA and Tricare Health System



By Eric W. Koleda

National Director, TreatNOW State Legislative Efforts
USAF Vietnam Era Veteran

January 6, 2022

Executive Summary

"All that a man hath he will give his life for his country … the soldier puts his life at stake, and often yields it up in his country's cause. The highest merit, then, is due the soldier" (Abraham Lincoln March 1864).

The soaring diabetes rates, and the associated lower limb amputations, across the globe have fueled prosthetics and wheelchair industries. There are **2.1 million people** living with limb loss in the USA, and that number is *expected to double* by 2050.[1] Our Veteran population is not immune to this reality. Diabetes is one of the most widespread chronic diseases in the United States yet is also one of the most ignored and underdiagnosed. The civilian population has relatively easy access to limb saving treatments including hyperbaric oxygen through commercial payers, Tricare, Medicare, and Medicaid. Hyperbaric Oxygen Therapy (HBOT) is a therapy proven to reduce amputations in patients with diabetic foot ulcers (DFU's) and is an approved indication by the FDA. CMS and even, Tricare. Our Veterans deserve the same ease of access to this life saving care, which is not the current situation. Despite recent efforts by the VA to improve access to community available care, the referral and reimbursement process continues to be overly burdensome and because of this, limits access. Providing routine HBOT services to diabetic DFU patients in both the VA, DoD and civilian communities is a proven treatment modality to improve DFU outcomes and reduce or prevent amputations. A standard course of HBOT has been shown to improve outcomes, reduce the need for amputations, while proving more cost effective that the amputation surgery and associated after-care (rehab, home health, physical therapy, durable medical equipment, and prosthetics). The VA system and Tricare in particular, should be able to realize significant cost savings over the short and long-term with the use of HBOT services for many of the FDA approved indications, but especially with DFU's as the financial analysis herein shows. HBOT treatments are estimated to be less than 13 percent of the cost for surgical, inpatient hospital stay and cost of care expense for DFU amputations (Table 8). That is the financial reality. Perhaps a more important reality is the decline in quality and length of life associated with loss of a limb.

In 2022, it is estimated the VA Diabetic Foot Ulcer (DFU) Lower Limb Amputations (LLAs) will have a $1.8 billion annual economic impact (Table 1). The surgical cost estimate of over $491 million and the cost of care after surgery estimate of $536 million accounts for approximately 65 percent of the total amputation cost in 2022 (Table 1). With an estimate of over 3.1 million diabetics in the VA, the projection for the next ten years will be for DFU LLAs to increase substantially from the current VA twenty-year average of 6,032 amputations per year. The cost escalation for surgical procedures and after care will not be sustainable long-term by insurance providers based on current trends. Diabetes and diabetes related lower extremity complications combined account for the third most costly disease burden.[2] Reducing and

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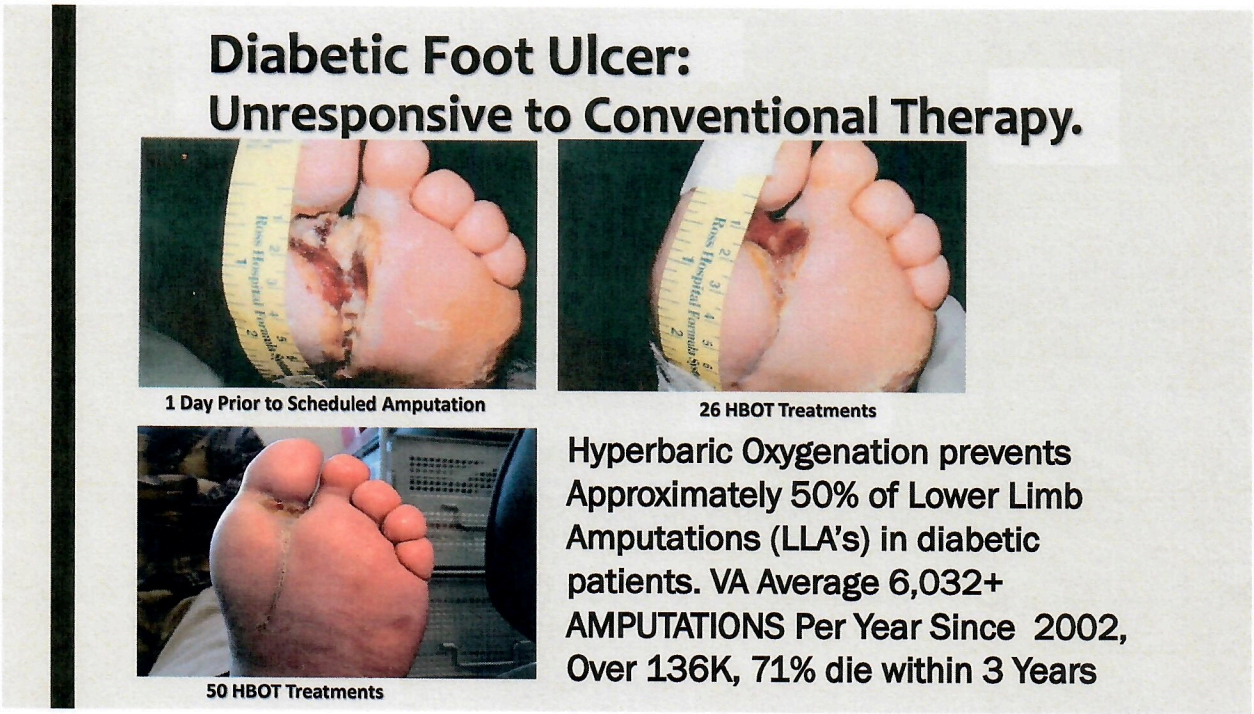
[1] Infor@AccessProsthetics.com; **15 Limb Loss Statistics that May Surprise You, October 18, 2017**

[2] Lazzarini, P. A., Pacella, R. E., Armstrong, D. G., & van Netten, J. J. (2018). Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. *Diabetic Medicine*, *35*(9), 1297-1299. https://doi.org/10.1111/dme.13680

sustaining even 50 percent of the amputations by treating with HBOT will have significant quality of life and financial benefits.

Among the overall US population, 2018 estimates were 34.2 million people of all ages, or 10.5 percent of the population had diabetes. An additional 34.1 million adults 18 years or older or 13 percent of all US adults, and 7.3 million adults were not aware or did not report having diabetes.[3] Seniors over 65 years of age account for 26.8 percent of the US population with diabetes.[4] Approximately 50-70 percent of the Veterans enrolled in the Veteran Administration Health network are diabetic. Approximately 25 percent of diabetics will develop a DFU in their lifetime, 56 percent of DFUs will become infected and one in five of those will require an amputation.[5] Approximately 85 percent of lower limb amputations are preceded by a foot ulcer.[6] Following Lower Limb Amputation (LLA), 50 percent will undergo contralateral amputation in two-five years. Patients undergoing a bilateral amputation due to a DFU, have a five-year mortality rate higher than rates for breast cancer, colon cancer, and prostate cancer combined.[7] Amputation is not just a life altering event, it has become a death sentence worse than cancer.



"The estimate in the US in 2007 was $18.9 billion spent on the care of diabetic foot ulcers and $11.7 billion on lower extremity amputations. It becomes a death sentence for 70.1 percent of DFU Veterans who are told amputation is the only option remaining. It is estimated lifetime healthcare costs for people with limb loss is $509,275 compared to $361,200 for people without

[3] Cdc.gov; National Diabetes Statistics Report 2020; Estimates of Diabetes and Its Burden in the United States
[4] Ibid.
[5] Amputation Prevention Center at Sherman Oaks Hospital; Diabetic Foot Ulcer Protocols; Lee C Rogers, D.P.M.
[6] Infor@AccessProsthetics.com; 15 Limb Loss Statistics that May Surprise You, October 18, 2017
[7] Infor@AccessProsthetics.com; 15 Limb Loss Statistics that May Surprise You, October 18, 2017

limb loss.[8] In 2013 numbers it was estimated hospital charges for patients who underwent amputation totaled $8.7 billion. The estimated cost to American private and public insurance agencies is $12 billion annually. We estimated since 2002 through 2022, slightly over 148,000 DFU amputations in the VA at an estimated cost of $9.8 billion for surgical procedures.. This is in addition to another $383.8 million in hospital after surgery costs for the average stay of 11-days (Table 1). Over 102,000 Veterans are estimated to have died within 3-years. The cost of care after amputation surgery is estimated to be $536.3 million in 2022 dollars (Table 1). When you dovetail in wheelchair costs at $117.1 million and prostheses cost at $58.3 million, the cost to treat DFUs with HBOT becomes an easy business decision. However, this should not be a financial decision alone.

The human costs of amputation are life changing. Most authors find the return-to-work rate for amputees to be about **66%** (from 43.5 to 100% for participants after lower limb amputation and 53–100% for people after upper limb amputation) [9]Considerations related to return-to-work depends on general factors, such as age, gender and educational level; factors related to impairments and disabilities because of amputation (amputation level, multiple amputations, co-morbidity, the reason for amputation, persistent stump problems, the time from the injury to obtaining a permanent prosthesis, wearing comfort of the prosthesis, walking distance and restrictions in mobility; rehabilitation; factors related to prosthesis; and factors related to work and policies (salary, higher job involvement, good support from the implementing body and the employer and social support network).Amputation wounds generally heal in four to eight weeks on average. Being permanently disabled and unemployed or unemployable is devasting.

Mortality rates following amputation patients ranges from 13 to 40 percent in year one, 35-70 percent in three years, and 38-80 percent in five years, making amputation worse than most malignancies.[10]Typical complications associated with amputations consist of heart problems such as heart attacks, deep vein thrombosis (DVT), slow wound healing and wound infection requiring a second amputation, pneumonia, and stump or "phantom limb" pain. Physical rehabilitation is an important aspect after amputation, but it can be long, difficult and a frustrating process for most patients.

The additional cost incurred include walking aids, wheelchair or scooter, prostheses limbs, if affordable or covered under medical insurance, assessing care and support needs, wheelchair ramps or stairlifts, special designed vehicles, physiotherapy denial, physical therapy, emotional stress such as depression, anxiety, grief and suicidal ideation, and PTSD. All these factors compound the financial impact over the expected average 2-5-year lifespan after amputation. We did not include all these additional humanistic costs into the analysis.

Since 2002, hyperbaric oxygen therapy has helped prevent amputations across America. Foot wounds are one of the most common complications of diabetes and are responsible for

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[8] Infor@AccessProsthetics.com: **15 Limb Loss Statistics That May Surprise You, October 18, 2017**

[9] Researchgate.net; Return to Work After Amputation, January 1970DOI:10.1007/978-0-387-87462-3_7; In book: Amputation, Prosthesis Use, and Phantom Limb Pain (pp.101-114)

[10] Ncbi.nim.nih.gov; Factors affecting lifespan following below-knee amputation in diabetic patients; October 5, 2017: 393-397

substantial morbidity.[11] Studies involving a significant number of patients have shown a high success rate in patients who had been unsuccessful with other modes of therapy.[12] "Of 1984 study records screened, 14 studies (768 participants) including twelve RCTs, and two CCTs were included as per inclusion criteria. The results with pooled analysis have shown that HBOT was significantly effective in complete healing of diabetic foot ulcer and reduction of major amputation."[13] This review provides evidence that hyperbaric oxygen therapy is safe and effective as an adjunct treatment measure for the foot ulcers and avoiding amputations inside and out of the VA.

The VA does not have an HBOT capability. Our research did not reveal widespread HBOT prescription and use by VA network providers. We also could not identify where DFU's are being routinely treated outside of the VA in the civilian HBOT facilities. In 2018 there were over 1,156 hospitals across the country equipped with hyperbaric oxygen chambers, and approximately 120 more private clinics. Assuming two monoplace chambers per facility, we estimate over 2,500 HBOT chambers available in the US. We did not include the facilities equipped with multi-place chambers to accommodate 2-20 patients at a time. There is adequate existing capacity for all DFU Veterans to be treated under the current VA policy and guidelines. With significant reduction in amputations being realized from treating with HBOT, the potential cost savings would be significant using the FDA, CMS, and Tricare approved treatment modality.

Hyperbaric Oxygen Therapy (HBOT) is approved by the FDA and CMS for 14 indications. Tricare has approved approximately nine of these treatment modalities, reflecting an industry and medical acceptance and use for decades. The medical benefits to patients across all approved indications has improved or saved lives. The approved HBOT indications have reduced long-term cost versus the conventional non-HBOT treatment approach over the full spectrum of FDA indications.

Hyperbaric Oxygen Therapy for DFUs has been an approved indication for almost two decades. It is also a cost-effective, proven treatment to reduce amputations, avoid related associated high post-surgery health costs, and significantly improve quality of life and length of Veterans lives. On the business side, providing HBOT outsource services and making treatments widely available to the VA patients and military service members, it will produce a high return on investment for Tricare providers. We can substantially lower overall healthcare costs while saving lives. Because of these financial, and more importantly human benefits, we ask that the VA system improve and actively promote access to community based hyperbaric centers to help save the lives and limbs of our Veteran population.

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[11] Washington State Health Care Authority; Hyperbaric Oxygen Therapy (HBOT) for Tissue Damage, Including Wound Care and Treatment of Central Nervous System Conditions; Final Evidence Report; 2013

[12] O2wny.com; Can HBOIT Help You Avoid Amputation? Craig Danehy, July 23, 2018

[13] Ncbi.nim.nih.gov; Efficacy of hyperbaric oxygen therapy for DFU, a systematic review and meta-analysis of controlled clinical trials;2021

TABLE 1

Cost Benefit Analysis of HBOT for DFU versus Amputation

(Cost estimates based on average of 6,032 Veteran amputations per year)

Estimated Annual Amputation Cost Impact

1.	Total estimated annual amputation surgical cost since ($9.8 billion/20 years= average cost year)	$491.0 Million
2.	Total estimated inpatient hospital stays cost (11 days)	$383.9 Million
3.	Total estimated three-year wheelchair cost	$225.6 Million
4.	Total estimated 2022 VA Cost of Care DFU patients	$536.3 Million
5.	Total estimated 2022 average annual Prostheses costs	$58.3 Million
6.	VA and Social Security disability payments per year	$111.9 Million
7.	Total estimated DFU amputations annual impact cost	**$1.8 Billion**

Estimated Annual HBOT Treatment Cost Wagner Grade III

1.	Estimated annual HBOT treatment cost 6,032 Vets (HBOT treatments based upon 2.0-2.5 ATA pressure For 120 minutes per day at $119 per 30 min segment And 6,032 Veterans per year)	**$181.2 million**

Estimated Annual Cost Savings Impact

1.	Estimated HBOT percent treatment to amputation	10%
2.	**Estimated annual cost savings (Minus disability payments)**	**$1.68 Billion**

Notes

Note 1: 1989-1998 data, Journal of Rehabilitation Research and Development, Vol 37, No 1, January/February 2000, Pages 23-30, Trends in lower limb amputation in the VA Health Administration

Note 2: FDA and CMS approved HBOT for diabetic Foot Ulcers in 2002 for DFU Wagner Grade III or higher

Note 3: Surgical cost escalated at 3.24% per year based on 114-year average US inflation rate

Note 4: Three-year mortality rate after amputation is 70.9% of patients

Note 5: 60-70% of hospitalized Veterans in US have diabetes

Note 6: Detailed analysis spreadsheets are available upon request to substantiate the herein above costs

Figueroa-Wright Neurology HBOT Evidence.pdf
Uploaded by: Robert Beckman
Position: FAV

Hyperbaric oxygen

B-level evidence in mild traumatic brain injury clinical trials

Xavier A. Figueroa, PhD
James K. Wright, MD, Col (Ret), USAF

Correspondence to Dr. Figueroa: bhif.figueroa@gmail.com

ABSTRACT

Objective: First, to demonstrate that B-level evidence exists for the use of hyperbaric oxygen therapy (HBOT) as an effective treatment in mild to moderate traumatic brain injury/persistent postconcussion syndrome (mTBI/PPCS). Second, to alert readers and researchers that currently used pressurized air controls (≥21% O_2, >1.0 ATA) are therapeutically active and cannot be utilized as sham controls without further validation.

Method: Review of published, peer-reviewed articles of HBOT prospective and controlled clinical trials of mTBI/PPCS symptoms.

Results: Published results demonstrate that HBOT is effective in the treatment of mTBI/PPCS symptoms. Doses of oxygen that are applied at ≥21% O_2 and at pressures of >1.0 ATA produce improvements from baseline measures. Some of the recently published clinical trials are mischaracterized as sham-controlled clinical trials (i.e., sham = 21% O_2/1.2–1.3 ATA), but are best characterized as dose-varying (variation in oxygen concentration, pressure applied, or both) clinical trials.

Conclusions: Hyperbaric oxygen and hyperbaric air have demonstrated therapeutic effects on mTBI/PPCS symptoms and can alleviate posttraumatic stress disorder symptoms secondary to a brain injury in 5 out of 5 peer-reviewed clinical trials. The current use of pressurized air (1.2–1.3 ATA) as a placebo or sham in clinical trials biases the results due to biological activity that favors healing. ***Neurology*® 2016;87:1–7**

GLOSSARY

DoD = Department of Defense; **HBA** = hyperbaric air; **HBO** = hyperbaric oxygen; **HBOT** = hyperbaric oxygen therapy; **mTBI** = mild traumatic brain injury; **PPCS** = persistent postconcussion syndrome; **PTSD** = posttraumatic stress disorder; **TBI** = traumatic brain injury; **VA** = Veterans Administration.

The use of hyperbaric oxygen (HBO) as a therapy for brain injuries has been tested infrequently and in a fashion not congruent with evidence-based medicine for many years. This has changed since 2008, with clinical trials testing HBO under sponsorship of the Department of Defense (DoD)/Veterans Administration (VA) and Army or under civilian initiative. The common purpose of these clinical trials was to assess the clinical efficacy of HBO therapy (HBOT) on postacute mild traumatic brain injury (mTBI)/persistent postconcussion syndrome (PPCS). Several earlier articles (pre-2010) have presented patient outcome studies[1–9] and retrospective analyses[10–12] that report positive effects of HBO on traumatic brain injury (TBI) and neurologic head injuries. Since 2012, a new series of clinical trials[13–19] have demonstrated that HBO has reparative effects for mTBI/PPCS symptoms and cognitive deficits.

Study results to date have been clouded by confusion regarding what constitutes an effective sham. Broadly divided, the DoD/VA/Army-sponsored trials utilized pressurized air groups as sham controls, while civilian-led studies utilized crossover designs or baseline comparators to assess improvement. Assumptions made on the use of certain controls by the DoD/VA/Army-sponsored studies has led some of the study authors to conclude no effect was present, when there was actually a significant improvement in primary and secondary endpoints.

From the Brain Health & Healing Foundation (X.A.F.), Seattle; and Swedish Medical Center (J.K.W.), Wound Healing & Hyperbarics, Edmonds, WA.
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

RESULTS OF THE HBOT CLINICAL TRIALS Four pivotal US-based clinical trials and one Israeli-based clinical trial have provided well-structured and controlled studies that demonstrate reparative effects in mTBI/PPCS symptoms with HBOT. Improvements in TBI and posttraumatic stress disorder (PTSD) symptom scores for the 2 DoD/VA-sponsored studies,[15,16,20] the Army-sponsored study of Miller et al.,[14] a civilian-sponsored study of Harch et al.,[18] and the Israeli civilian study of Boussi-Gross et al.[19] have demonstrated both clinical and statistically significant improvements from baseline measures after undergoing 30–40 1-hour HBOT treatments during the course of the trials. All participants had documented TBIs and were at least 2 years into the PPCS phase of the injury, ensuring that spontaneous recovery was a highly unlikely factor.

The DoD/VA/Army[14–16,20] and civilian[18] studies provide valuable cross-study comparable measures in 4 reported clinical trials. The Rivermead Post-Concussion Questionnaire, Immediate Post-Concussion Assessment and Cognitive Testing, and PTSD Checklist–Military were used as primary and secondary endpoint measures in all the US studies. Although the DoD/VA/Army-sponsored study authors characterize their studies as sham-controlled, the studies are best classified as dose-and-pressure-varying trials. When analyzed as individual groups, the results (figure 1, left) are scattershot and uninformative. However, a dose curve emerges when the study results are arranged by the amount of relative dissolved oxygen that participants experienced (figure 1, right), a clear indication that HBOT is having a drug-like effect in brain injury repair. The graphs on the right (figure 1) are grouped into relative levels of dissolved oxygen in plasma. The numbers under each group (1, 1.15, 8.6, 11.5, and 13.75) represent the multiplier of the average amount of dissolved oxygen above 1.0 ATA, 21% O_2 that is in the plasma (e.g., −8.6 is 8.6 times greater than the amount of plasma dissolved at 1.0 ATA, 21% O_2).

The clinical improvements seen in the participants are large and consistent through each of the studies. The apparent dose response profile strongly suggests that lower pressures (≤2.0 ATA) and lower oxygen levels (<100% O_2) are potentially better for mTBI/PPCS and PTSD symptom recovery. Like prescription drugs, there is a Goldilocks zone when using HBOT (or hyperbaric air [HBA]) for treating mTBI/PPCS: too much may impair repair mechanisms; too little may not provide sufficient support; just right ensures that repair mechanisms are optimized.

The use of unproven shams has led to conclusions of inactivity in the current literature. For example, the published articles by Wolf et al.,[20] Cifu et al.,[15,16] and Miller et al.[14] contended that the observed improvements of HBOT (and HBA) were a placebo effect due to the ritual of HBO.[21] Yet the controls that were applied to these studies have known biological activity.[22] A recurrent objection by study authors that incorrectly assumed the control groups they selected were inactive is best exemplified in the following:

> We recognize that a sham is not inert, and we cannot completely discount the physiological effects of minimal increases in nitrogen or oxygen from pressurized room air. However, we believe it is biologically implausible that air at 1.2 ATA (equivalent to 2 m of seawater pressure) has a beneficial effect on healing the damaged brain remotely after mTBI.[14]

Positive improvements from pretreatment (baseline) measures are observed in all the DoD/VA/Army and civilian studies. The measured responses to both HBO and HBA treatment groups are therapeutic, but a minimal effective dose of O_2 + pressure has not been established in the hyperbaric medical literature. Thus, the use of a sham is problematic and confounding for study interpretation.

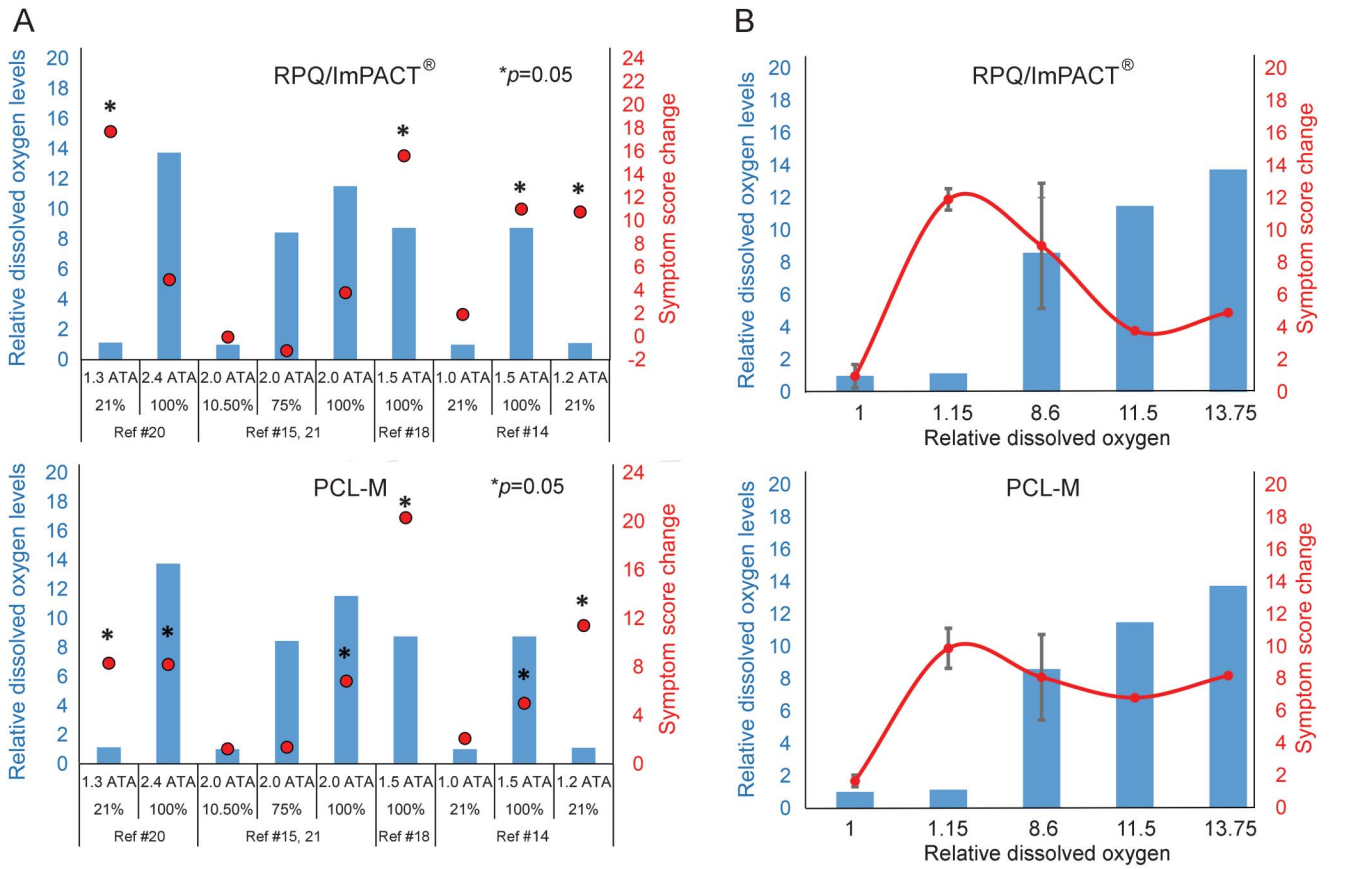
Dr. E. George Wolf,[20] lead author of the first published work of the DoD/VA-sponsored studies, clarified his position on his original conclusion[13] and conceded that the controls used in his study might be active and bias the conclusions of the study. He noted the following:

> Placebo effect in our previous reports has been considered as why there was no significant statistical difference in this study…However, both groups showed improvement in scores and thus a benefit. Given the studies demonstrating hydrostatic pressure effects and results of Boussi-Gross' crossover study, our design could be considered a treatment comparison vs a true sham with a therapeutic effect from both increased oxygen partial pressure and hydrostatic pressure. A Type II statistical error cannot be ruled out…There is a potential gain and no potential loss. The VA/Clinical Practice Guidelines define a "B evidence rating" as "a recommendation that clinicians provide (the service) to eligible patients." At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.[13]

There is a substantial body of evidence that demonstrates the biological activity of pressurized air (see Biological effects of pressurized gases). The consistency of improvement affirms the therapeutic effect of HBOT on mTBI/PPCS (figure 1). Given the consistent improvement reported in recent clinical trials (a total of 5 out of 5 studies demonstrate a statistically significant improvement in one or both primary outcome measures posttreatment) and the excellent safety record of hyperbaric treatment, HBOT should be prescribed for mTBI/PPCS.

DISCUSSION **Biological effects of pressurized gases.** As mentioned earlier, we countered that it was incorrect

Figure 1 Changes in average symptom score (pre- vs post-HBOT) and dissolved oxygen in plasma



Results of the Department of Defense/Veterans Administration studies, the Army-sponsored studies, and the Harch et al.[18] civilian study. (A, left column) Total points change in score values from baseline assessment tests in traumatic brain injury symptom scores (top) and the PTSD Checklist–Military outcome scores (bottom). Outcomes are grouped by publication source. (B, right column) Outcome values from the left graphs grouped by relative dissolved oxygen levels. 1 = 1.0 ATA, 21% O_2 equivalents (Miller et al.[14] and Cifu et al.[15,16]; N = 44). 1.15 = 1.2 and 1.3 ATA, 21% O_2 (Miller et al.[14] and Wolf et al[20]; N = 49). 8.6 = 1.5 and 1.5 ATA, 100% O_2/2.0 ATA, 75% O_2 (Harch et al.,[18] Miller et al.,[14] Cifu et al.[15,16]; N = 58). 11.5 = 2.0 ATA, 100% O_2 (Cifu et al.[15,16]; N = 21). 13.75 = 2.4 ATA, 100% O_2 (Wolf et al.[20]; N = 24). Error bars are standard deviation. Red dots are the average symptom scores. Blue bars are dissolved oxygen levels. HBOT = hyperbaric oxygen therapy; ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; RPQ = Rivermead Post-Concussion Questionnaire.

when the DoD/VA/Army-sponsored studies utilized pressurized air as a control group (they labeled them sham comparators). The use of an air group was based on the assumption that pressures below 1.4 ATA and oxygen concentration of 21% O_2 would have minimal to no effect. The literature in experimental biology and preclinical animal models is extensive, and demonstrates that low-pressure pure oxygen or low-pressure medical grade air induce biologically measurable and therapeutic responses.

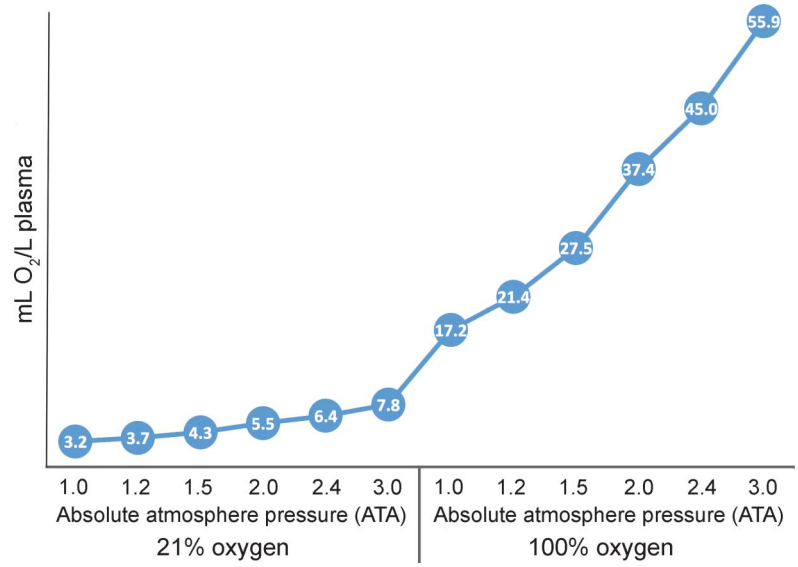
The clearest example to date that demonstrates that these gas/pressure combinations have a therapeutic effect on brain injury models is the article by Malek et al.[22] They demonstrated that HBO (100% O_2) and HBA (21% O_2/79% N_2) were equivalent in protecting neurons after transient forebrain ischemia in the gerbil using 2.5 ATA. Gerbils were induced to undergo ischemia and then treated (HBO, HBA, or normobaric oxygen), not treated, or given a sham surgery without inducing ischemia. No statistically significant difference between HBO and HBA was observed in neuronal protection; both were equally effective in protecting against neuronal loss when compared to the ischemic group. Malek et al. suspected that pressurized air had therapeutic potential and therefore compared all treatment groups against a sham surgical control. The role of a potential placebo effect was ruled out in this study and demonstrates the activity of HBO and HBA in a neurologic injury model.

HBA and low-pressure HBO (≤1.2 ATA) also have shown repeated biological effects in cell culture studies[23–25] and clear differential effects when applying HBO (2.4 ATA, 21% O_2)[26] vs pressure alone (2.4 ATA, 8.8% O_2; 21% O_2 equivalent) or oxygen alone (1.0 ATA, 100% O_2). There appears to be a threshold of oxygen concentration that is required for producing a biological response when greater than atmospheric pressure is applied. This reliance on increased pressure to elicit a biological response appears to be cell type

independent.[27] These results suggest a combination of oxygen + pressure is critical to achieving a biological response, even with pressures that are thought to be trivial or noneffective. No systematic, in-depth analysis of the minimally effective oxygen concentration, coupled to increases (or decreases) in absolute pressure, have been undertaken in animal or cell culture studies. Although important to the understanding of potential mechanisms of action for HBOT and HBA, the current results should not be dismissed as a placebo or Hawthorne effect. Ideally, a dose-response curve with an animal model would help to delineate the observed effects of pressurized oxygen and nitrogen, establishing the rationale for a true sham.

Animal studies demonstrating the effects of a threshold level of oxygen + pressure are equally revealing in the areas of muscle injury repair in rats. Small increases in pressure ([1.25 ATA, 100% O_2] vs [1.0 ATA, 100% O_2])[28] induce accelerated repair. Changes in insulin/glucose response and muscle force twitch were observed in the pressure group (1.25 ATA, 36% O_2), but not in the pure oxygen group (1.0 ATA, 100% O_2).[29,30] Furthermore, the protective effects of HBA (2.5 ATA, 21% O_2) on cerebral heatstroke[31] only worked when pressure was applied. The notion that low-pressure pure oxygen or high-pressure air can be a sham is not supported by the cell culture and animal data. Furthermore, there are unresolved issues associated with tissue sensitivity and responses to changes in dissolved oxygen concentration in humans. What is good for wound healing at skin and skeletal muscle levels (which are hypoxia-tolerant) may not be the same for neural or cardiac tissue (which are hypoxia-sensitive).

Figure 2 **Levels of dissolved oxygen in plasma (mL O_2/L plasma) at varying oxygen concentrations and pressures of hyperbaric air and oxygen**



One key question that remains in the hyperbaric medical literature is a unifying mechanism of action to carry out the observed effects of gases delivered at pressures greater than 1.0 ATA. As displayed in figure 2, levels of dissolved oxygen in plasma vary by pressure and the % oxygen levels in the breathed fraction. Breathing 100% O_2 at 1.0 ATA delivers far more dissolved oxygen than breathing air at 3.0 ATA of 21% O_2. Yet 100% O_2 at 1.0 ATA does not have the same effect for TBI or ischemic models of injury as 1.2 or 1.5 ATA of 21% O_2. A great deal of research and new thinking must be applied to understand what is really happening to explain the animal and clinical data we are seeing with HBA and HBO. The lack of an identifiable mechanism does not invalidate the observed effects.

Hyperbaric medicine has gone through a contentious history,[32] with editorials characterizing hyperbaric medicine as "A therapy in search of diseases,"[33] editorial opinions discounting biological effects of pressurized air,[34,35] and studies that assume little or no biological activity of a pressurized air "control."[14–16,36,37]

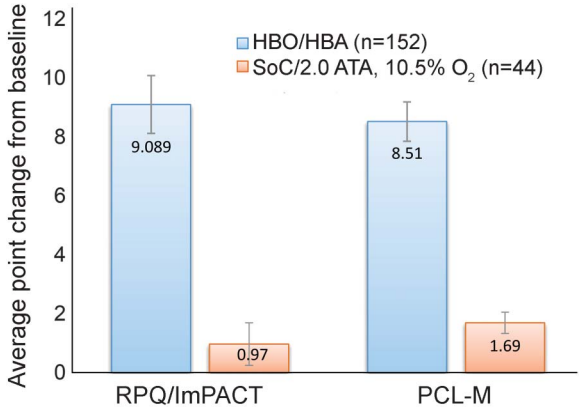
In all the published studies, patients with mTBI/PPCS improved from their baseline values in a measurable, consistent manner and in excess of what is seen with available local care for mTBI/PPCS.[14,19] These improvements were consistent in 4 independent US-based studies and even with weighted averages applied, the results are large and significant (figure 3). The heterogeneous nature of a TBI should not bias the physician from overlooking the ability of HBO (or HBA) in assisting or accelerating repair of the brain. HBOT has accumulated a rather large body of evidence on the myriad biochemical, physiologic, and cellular effects that it can elicit[38–40] to induce repair in the body.

It is important to remember that the improvements reported with the reviewed mTBI/PPCS trials occur years after medical consensus opinion believes that improvements of this magnitude can occur. When reviewing the published studies, one must accept that variable doses are being applied and no validated sham controls are present. This fundamentally shifts the interpretation of data in these studies.

The criteria established by the editors of *Neurology*®[41–43] state the following for B-level evidence: "Level B rating requires at least 1 Class I study or 2 consistent Class II studies." The current literature presents at least B-level evidence for the use of HBOT to treat the symptoms of mTBI/PPCS and PTSD secondary to an mTBI:

1. Four Class I studies on the use of HBOT on mTBI/PPCS show a positive outcome when baseline and posttreatment outcome measures are compared objectively and without assumptions of inactivity from the control groups.

Figure 3 **Weighted aggregated averages of the Department of Defense/ Veterans Administration, Army, and civilian studies**



Hyperbaric oxygen (HBO) and hyperbaric air (HBA) at 1.2–2.4 ATA produce improvements that are superior to the combined standard of care (SoC) or the 21% oxygen equivalent concentration control (10.5% oxygen at 2.0 ATA) values. Error bars are SD. ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; PCL-M = PTSD Checklist-Military; RPQ = Rivermead Post-Concussion Questionnaire.

   a. The studies by Miller et al.,[14] Cifu et al.,[15,16] Wolf et al.,[20] and Boussi-Gross et al.[19] meet all the criteria for Class I evidence (neurology.org/site/misc/TableClassificationScheme.pdf).
2. One Class III study on the use of HBOT on mTBI/PPCS shows a positive outcome.
   a. The study by Harch et al.[18] used well-defined natural history records, with patients serving as their own controls. Pretreatment and posttreatment testing were independently assessed and derived by objective outcome measures.[18] All participants experienced statistically significant symptom improvements for TBI and PTSD measures.

It would be a great loss to clinical medicine to ignore the large body of evidence collected so far that consistently concludes that HBO is effective in treating brain injuries.

The need for further studies is an often-made statement in clinical research, but if further research is to be attempted in the area of HBOT for neurologic injuries, the use of pressurized shams should be avoided, until such a time that a true sham has been identified. Furthermore, HBOT should be made available as an adjunct to standard of care for mTBI/PPCS treatment, as clinical application can allow for information capture in a national database and treatment parameters refined by application and experience.

The placebo effect and Hawthorne effects purported to exist in the studies must be addressed. The ongoing debate and lack of clear information as to what may constitute an effective sham must account for both pressure and oxygen levels (nitrogen, as well). An adequate sham group in a clinical trial would, at minimum, be required to enter a hyperbaric chamber, spend an equivalent time as the treatment group inside the chamber, breathe room air, and not undergo pressurization. Ensuring a double-blind becomes difficult, but not impossible to achieve with this type of sham.

The Hawthorne effect may play a role in the outcomes of the published clinical trials in HBOT, but participation in a validated sham group would help control for that effect. If shams are not to be used in future HBOT trials, it is recommended that study participants randomized to the control group undergo the same treatment at the hands of the clinic as HBOT interventions group sans exposure to a chamber. This would require that control participants attend a study site at a fixed time during the day and perform the same tasks as the HBOT treatment participants. In most cases, active arm participants are allowed to watch movies, read, or listen to music in either a multiplace or monoplace chamber. Having the same activities for Hawthorne control group as the HBOT treatment group should suffice. If the improvement attributed to a placebo or Hawthorne effect is significant, which some researchers say is the case, it is surprising that no one appears to have endorsed this as a treatment for TBI or attempted to replicate the outcome in a parallel study.

Finally, a Food and Drug Administration sanction should be sought for future studies and the NIH should be strongly encouraged to revisit HBO as a potential therapy and provide funding for definitive phase III trials, under the guidance and oversight of national and international monitors. The implications of HBOT for neurologic recovery and repair have far-reaching consequences in the medical fields of neurology and rehabilitation medicine and for public health in general. Important in this proposed phase III study for mTBI/PPCS is the need to properly diagnose study participants and use both objective and subjective pre- and post-baseline measures.

For objective measures, at a minimum PET or SPECT would provide a clear picture of metabolic and blood flow changes to the brain of injured subjects. MRI technologies, such as diffusion tensor imaging and functional MRI, would be ideal, but expensive and limited by the number of machines of enough field strength to provide imaging. Subjective measures are an important tool for assessing clinically meaningful changes in study subjects. The use of symptom questionnaires that are specific to mTBI/PPCS, general health and attitude surveys, and cognitive tests that measure established neurologic deficits in this population should be used. Computerized assessment systems provide unbiased, timed, and altered forms for repeat testing of this population.

Furthermore, a national database should be created for physicians and hyperbaric clinics to deposit treatment data for individuals who are using HBOT for mTBI/PPCS. The current loss of data on outcomes of self-paying or pro bono treatments needs to be captured with an organized and standardized system of data gathering. People are using this therapy and it is a tremendous waste of resources not to derive meaningful health outcome information from this population.

There is sufficient evidence for the safety and preliminary efficacy data from clinical studies to support the use of HBOT in mTBI/PPCS. The reported positive outcomes and the durability of those outcomes has been demonstrated at 6 months post HBOT treatment.[18] Given the current policy by Tricare and the VA to allow physicians to prescribe drugs or therapies in an off-label manner for mTBI/PPCS management and reimburse for the treatment, it is past time that HBOT be given the same opportunity. This is now an issue of policy modification and reimbursement, not an issue of scientific proof or preliminary clinical efficacy.

AUTHOR CONTRIBUTIONS

Dr. Figueroa developed the review concept and design, collected the data, analyzed and interpreted the data, and supervised the study. Dr. Wright provided critical revisions of the manuscript and important intellectual content and provided additional interpretation to the data analysis. Both authors contributed time, funds, and effort in preparing this manuscript.

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DISCLOSURE

X. Figueroa is a scientific and technical consultant for Nativis, Inc. (60%), ENG[3] (10%), and Cytokinetics (15%). He volunteers his time as the President of the Brain Health & Healing Foundation and writes for the Foundation's blog. J. Wright is an employee of Swedish Medical Center (Edmonds), Wound Healing and Hyperbarics, were he performs in a clinical practice (100%) and bills for his procedures. He volunteers his time as a member of the Science Advisory Board for the Brain Health & Healing Foundation. Go to Neurology.org for full disclosures.

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MOST RECENT RESEARCH SHOWING THE SAFETY AND EFFICACY OF HBOT FOR TBI/PTSD

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concussion, there is no consensus for treatment of chronic symptoms. Moreover, most of the pharmacologic and non-pharmacologic treatments have failed to demonstrate significant efficacy on both the clinical symptoms as well as the pathophysiologic cascade responsible for the permanent brain injury. This article reviews the pathophysiology of PCS, the diagnostic tools and criteria, the current available treatments including pharmacotherapy and different cognitive rehabilitation programs, and promising new treatment directions. ***A most promising new direction is the use of hyperbaric oxygen therapy, which targets the basic pathological processes responsible for post-concussion symptoms; it is discussed here in depth.***

[19] Wang F, et al. *Hyperbaric oxygen therapy for the treatment of traumatic brain injury: a meta-analysis.* Neurol Sci. 2016 Jan 8. PubMed PMID: 26746238. **"Compelling evidence suggests the advantage of hyperbaric oxygen therapy (HBOT) in traumatic brain injury. ...Patients undergoing hyperbaric therapy achieved significant improvement....with a lower overall mortality, suggesting its utility as a standard intensive care regimen in traumatic brain injury."**

[20] E.G. Wolf, L.M. Baugh, C.M.S. Kabban, et al. ***Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial.*** UHM 2015, Vol. 42, No. 4, 2015. Dr. Wolf is a principle co-author of the first Army study. This recent USAF paper reanalyzing the data in the cornerstone DOD/VA/Army study concludes: "This pilot study demonstrated no obvious harm [and] both groups showed improvement in scores and thus a benefit. Subgroup analysis of cognitive changes and PCL-M results regarding PTSD demonstrated a relative risk of improvement . . . . There is a potential gain and no potential loss. The VA/Clinical Practice Guidelines define a "B evidence rating" as "a recommendation that clinicians provide (the service) to eligible patients. ***At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm***. . . .[emphasis added] Hyperbaric oxygen therapy for mild traumatic brain injury and PTSD should be considered a legitimate adjunct therapy if future studies demonstrate similar findings or show comparable improvement to standard-of-care or research-related treatment modalities." [NOTE: subsequent worldwide studies already published and those underway show comparable improvements.] ***http://bit.ly/2faBldN***

[21] Leila H Eadie (editorial). ***New technology and potential for telemedicine in battlefield brain injury diagnostics.*** Concussion (2016) 1(4), CNC22. **"**In severe cases, [TBI] injury occurs due to bleeding and inflammation, having several different effects: contact with blood causes brain tissue to swell (cerebral edema), and pooled blood within the confines of the skull also puts pressure on nearby tissue, constricting blood flow and depriving the brain of oxygen, killing neurons and leading to a chemical cascade that reinforces the injury. . . . People suffering from TBI can deteriorate suddenly and die, and in some cases swift treatment can help reduce mortality. Others will have minor initial symptoms, yet untreated brain hemorrhage can have insidious long-term effects. The etiology of postconcussive syndrome is debated, but may be caused by diffuse axonal injury or persistent metabolic alterations resulting in neuronal dysfunction and develops in 38–80% of patients with TBI...."

[22] Christine L. Mac Donald, Jason Barber, Mary Jordan, Ann M. Johnson, Sureyya Dikmen, Jesse R. Fann, Nancy Temkin. **Early Clinical Predictors of 5-Year Outcome After Concussive Blast Traumatic Brain Injury**. *JAMA Neurology*, 2017; DOI: 10.1001/jamaneurol.2017.0143 "Together these findings indicate progression of symptom severity beyond one year after injury . . . . We believe that by being informed from longitudinal studies such as this one, the medical community can be proactive in combating the potentially negative and extremely costly effect of these wartime injuries."

[23] *Daniel Nicoara, Raymond M. Quock et al.* ***Hyperbaric oxygen treatment suppresses withdrawal signs in morphine-dependent mice.*** *Brain Research, 2016; 1648:434* *DOI:*10.1016/j.brainres.2016.08.017 Groundbreaking research from Washington State University found that hyperbaric oxygen treatment (HBOT) can halve the pain and symptoms of opiate withdrawal/detox.

1. Other Peer-reviewed published articles

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[b] Malek M, et al. **Hyperbaric oxygen and hyperbaric air treatment result in comparable neuronal death reduction and improved behavioral outcome after transient forebrain ischemia in the gerbil.** *Experimental Brain Research Experimentelle Hirnforschung Experimentation Cerebrale*. 2013;224(1):1-14. doi:10.1007/s00221-012-3283-5.

[c] Fife CE, Eckert KA, Carter MJ**. An Update on the Appropriate Role for Hyperbaric Oxygen: Indications and Evidence**. *Plast Reconstr Surg*. 2016;138(3 Suppl):107S-16S.

[d] Shi XY, Tang ZQ, Sun D, He XJ. Evaluation of hyperbaric oxygen treatment of neuropsychiatric disorders following traumatic brain injury. Chin Med J (Engl). 2006;119(23):1978-82. http://www.ncbi.nlm.nih.gov/pubmed/17199942

[e] Hardy P, Johnston KM, De Beaumont L, Montgomery DL, Lecomte JM, Soucy JP, et al. Pilot case study of the therapeutic potential of hyperbaric oxygen therapy on chronic brain injury. J Neurol Sci. 2007;253(1-2):94-105. http://www.ncbi.nlm.nih.gov/pubmed/17234213

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[g] Wright JK, Zant E, Groom K, Schlegel RE, Gilliland K. Case report: Treatment of mild traumatic brain injury with hyperbaric oxygen. Undersea Hyperb Med. 2009; 36(6):391-9. http://www.echa.net/36-6%20UHM-P391-399.pdf

[h] Harch PG, Fogarty EF, Staab PK, Van Meter K. Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post traumatic stress disorder: a case report. Cases J. 2009;2:6538. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2740054/

[i] Rockswold, Rockswold, Zaun and Liu. A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. *Journal of Neurosurgery, Jun 2013 / Vol. 118 / No. 6 / Pages 1317-1328* *http://www.ncbi.nlm.nih.gov/pubmed/23510092*

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[k] Paul G. Harch, Susan R. Andrews, Edward F. Fogarty, Daniel Amen, John C. Pezzullo, Juliette Lucarini, Claire Aubrey, Derek V. Taylor, Paul K. Staab, and Keith W. Van Meter. A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. J Neurotrauma. 2012 Jan 1;29(1):168-85. http://online.liebertpub.com/doi/pdf/10.1089/neu.2011.1895

[l] Stoller KP. All the right moves: the need for the timely use of hyperbaric oxygen therapy for treating TBI/CTE/PTSD. Medical Gas Research. 2015;5:7. doi:10.1186/s13618-015-0028-0.

[m] Stoller KP. Hyperbaric oxygen therapy (1.5 ATA) in treating sports related TBI/CTE: two case reports. Med Gas Res. 2011;1(1):17. PMCID: 3231948. http://www.medicalgasresearch.com/content/pdf/2045-9912-1-17.pdf

[n] Lei Huang and Andre Obenaus. Hyperbaric oxygen therapy for traumatic brain injury Medical Gas Research, September 6, 2011.

2. Peer-reviewed Israeli research on stroke and TBI, neurogenesis and angiogenesis

[1] Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0079995

[2] Hyperbaric Oxygen Induces Late Neuroplasticity in Post Stroke Patients - Randomized, Prospective Trial http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0053716

[3] Hyperbaric oxygen may induce angiogenesis in patients suffering from prolonged post-concussion syndrome due to traumatic brain injury. Restor Neurol Neurosci. 2015 Oct 7. http://www.ncbi.nlm.nih.gov/pubmed/26484702

[4] Hyperbaric oxygen can induce neuroplasticity and improve cognitive functions of patients suffering from anoxic brain damage. Restorative Neurology and Neuroscience 33 (2015) 471–486 http://www.ncbi.nlm.nih.gov/pubmed/26409406

[5] Reflections on the neurotherapeutic effects of hyperbaric oxygen http://informahealthcare.com/doi/pdf/10.1586/14737175.2014.884928

3. Animal studies showing positive effects of HBOT on brain injury

[a] Kent MacLaughlin, et al. **The Effect of Intermittent Normobaric Hyperoxia on Stem Cell Mobilization and Cytokine Expression**. Report of research conducted at University of Wisconsin and reported at HBOT2018, Denver, CO, August 2018. Together these findings support the likelihood of biologic activity, consubstantial with HBOT, being activated at much lower dose of hyperoxia than previously postulated. The results demonstrate that the Army's and UHMS's claims

that hyperbaric medicine only occurs at pressures higher than 1.4ata are fallacious. Any increase in oxygen concentration and/or pressure is a medical intervention.

[b] Blast Exposure Induces Post Traumatic Stress Disorder-Related Traits in a Rat Model of Mild Traumatic Brain Injury. Gregory A. Elder, Nathan P. Dorr, Rita De Gasperi, Miguel A. Gama Sosa, Michael C. Shaughness, Eric Maudlin-Jeronimo, Aaron A. Hall, Richard M. McCarron, and Stephen T. Ahlers. Journal of Neurotrauma. http://online.liebertpub.com/doi/abs/10.1089/neu.2012.2510

[c] Research Report: Hyperbaric oxygen therapy improves spatial learning and memory in a rat model of chronic traumatic brain injury. Paul G. Harch, Christopher Kriedt, Keith W. Van Meter, Robert James Sutherland, BRAIN RESEARCH 1174 (2007) 120-129. http://www.researchgate.net/publication/5971941_Hyperbaric_oxygen_therapy_improves_spatial_learning_and_memory_in_a_rat_model_of_chronic_traumatic_brain_injury

[d] The effect of hyperbaric oxygen on intracephalic angiogenesis in rats with intracerebral hemorrhage. Peng ZR, Yang AL, Yang QD. J Neurol Sci. 2014 May2. http://www.ncbi.nlm.nih.gov/pubmed/24836574

[e] Kraitsy K, Uecal M, Grossauer S, Bruckmann L, Pfleger F, et al. (2014) Repetitive Long-Term Hyperbaric Oxygen Treatment (HBOT) Administered after Experimental Traumatic Brain Injury in Rats Induces Significant Remyelination and a Recovery of Sensorimotor Function. PLoS ONE 9(5): e97750. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0097750

[f] Calvert, Zhou, Nanda, and Zhang. Effect of hyperbaric oxygen on apoptosis in neonatal hypoxia-ischemia rat model. J Appl Physiol 95: 2072–2080, July 21, 2003.

4. Expert Opinion

[a] Richard A. Neubauer, M.D. and William S. Maxfield, M.D. **The Polemics of Hyperbaric Medicine.** Journal of American Physicians and Surgeons, Vol. 10 Number 1 Spring 2005, 15-17 www.jpands.org

[b] **Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations: Final Assessment.** The National Academies. The Institute of Medicine. Washington DC: The National Academies Press, 2014. https://bit.ly/2oYJ17l Significant finding: "DoD and VA are spending substantial time, money, and effort on the management of PTSD in service members and veterans [$9.3Billion+ through 2014]. Those efforts have resulted in a variety of programs and services for the prevention and diagnosis of, treatment for, rehabilitation of, and research on PTSD and its comorbidities. ***Nevertheless, neither department knows with certainty whether those many programs and services are actually successful in reducing the prevalence of PTSD in service members or veterans and in improving their lives."***

[c] **"What the *Bleep* is going on with Hyperbaric Oxygen Therapy?** Brain Health and Healing Foundation. Xavier Figueroa. PhD has been performing neurological clinical research since 1995 in the field of Alzheimer's research, as well as basic research in neuron biology, cancer research, bioengineering and the biophysics of water in cells. He has a long history of involvement with research using hyperbaric oxygen therapy for brain injury.
**http://brainjury.org/blog/2014/05/01/what-the-bleep-is-going-on-with-hyperbaric-oxygen-therapy/
**http://brainjury.org/blog/2014/07/03/what-the-bleep-is-wrong-with-the-dodva-hbot-studies/

**http://brainjury.org/blog/2014/11/23/what-the-is-going-on-with-hyperbaric-oxygen-therapy-part-3/

[d] UHM 2012, Vol. 39, No. 4 – How many deaths will it take? AN EDITORIAL PERSPECTIVE. Undersea & Hyperbaric Medical Society, Inc***. How many deaths will it take till they know?*** Monkeys, madmen and the standard of evidence. George Mychaskiw II, DO, FAAP, FACOP, Editor-in-Chief Chair, Department of Anesthesiology, Nemours Children's Hospital, Orlando, Florida USA. The Journal of Hyperbaric Medicine is the most prestigious journal on Hyperbaric Medicine in the world. . . . . ."Hyperbaric oxygen is a safe, easily used treatment that, in many cases, has resulted in a dramatic improvement in the symptoms of patients with [TBI]. Every day we are…. gathering more data validating its efficacy…. I feel, as do many of my colleagues, that there is sufficient clinical and research evidence to justify the use of [HBOT] as a standard-of-care treatment for [TBI] that should be reimbursed by CMS and Tricare…. I have no doubt that, over the next several years, [HBOT] will be proven beyond a reasonable doubt to be one of the most effective treatments for [TBI]…. There is a preponderance of evidence now to justify the use and funding for the treatment…." http://www.therapiehyperbare.com/images/hyperbare/2012-06_uhms_editorial.pdf

[e] **Chamber of Hopes for Brain Repair**. Eshel Ben-Jacob , PhD. January, 27, 2013. http://www.assafh.org/sites/en/Documents/Chamber%20of%20Hopes%20for%20Brain%20Repair.pdf

[f] **Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy.** Paul G. Harch. Medical Gas Research (2015) 5:9 DOI 10.1186/s13618-015-0030-6

[g] **Hyperbaric Oxygen Therapy for Brain Injury, Cerebral Palsy, and Stroke.** Summary, Evidence Report/Technology Assessment: Number 85. AHRQ Publication Number 03-E049, September 2003. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/clinic/epcsums/hypoxsum.htm

5. Data from DoD/Army studies, with responses

Summary of positive findings in Army Studies: Army medicine has run trials investigating the use of Hyperbaric Oxygen to treat and help heal Traumatic Brain Injury. They have shown that HBOT is both safe and effective: "***Randomization to the chamber . . . . offered statistical and in some measures clinically significant improvement over local routine TBI care.***" Also: ".... ***total scores for [both] groups revealed significant improvement over the course of the study for both the sham-control group .... and the HBO2 group***....." Expert outside consultants to DOD declared that ***"[HBOT] is a healing environment."*** The Army's premier researcher, Dr. Scott Miller, says on the Veterans Affairs web site: ***"People did get better and we can't ignore those results."***

[1] ***A randomized trial of hyperbaric oxygen in U.S. Service Members with post-concussive symptoms*** [BIMA]. Weaver et al. 2017. ***http://bit.ly/2x6d2EN***

[2] E.G. Wolf, ***Traumatic Brain Injury and Hyperbaric Oxygen Therapy: Dawn of a New Day.*** Presented at APWCA 16th Annual National Clinical Conference, 7-9 Sep 17. ***http://bit.ly/2x8WDiT***

[3] E.G. Wolf, L.M. Baugh, C.M.S. Kabban, et al. ***Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial.*** UHM 2015, Vol. 42, No. 4, 2015.

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http://biawa.org/docs/pdf/MTBI%20PCS%20J%20Neurotrauma%202012.pdf

[5] Paul G. Harch, MD. Letters to the Editor. Journal of Neurotrauma. **Hyperbaric Oxygen Therapy for Post-Concussion Syndrome: Contradictory Conclusions From a Study Mischaracterized as Sham-Controlled.** 2014 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3837504/

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[11] Army Trials Report from UHMS Conference, June 2013. Press Release: " DoD announces results of first three DoD-Sponsored trials using hyperbaric oxygen for mild traumatic brain injury." Available upon request.

[12] R. Scott Miller, M.D., COL, US Army, Director, Hyperbaric Oxygen Research Program, US Army Medical Materiel Development Activity, Ft. Detrick, MD. ***Effects of Hyperbaric Oxygen on Symptoms and Quality of Life Among Service Members With Persistent Postconcussion Symptoms.*** *JAMA Intern Med.* doi:10.1001/jamainternmed.2014.5479. Published online November 17, 2014.

6. Additional Relevant Science and Brain Wound Research.

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Johns Hopkins reports that the brains of Iraq and Afghanistan combat veterans who survived blasts from improvised explosive devices and died later of other causes show a honeycomb of broken and swollen nerve fibers in critical brain regions, including those that control executive function. The pattern is different from brain damage caused by car crashes, drug overdoses or collision sports, and may be the never-before-reported signature of 'shell shock' suffered by World War I soldiers.
http://www.sciencedaily.com/releases/2015/01/150114140600.htm

Blast injury, and the accompanying role of air embolism in invisible wounds to the brain, is still not widely studied and thus seldom treated. Hyperbaric Oxygen Therapy is recognized worldwide as the definitive treatment for air embolism. Air/gas embolism is already an on-label, approved indication for HBOT.

This is a page out of the Textbook of Military Medicine, updated in 2006; this same algorithm is in the textbook in the 1980s. The "definitive therapy" then and is HBOT treatment for TBI.

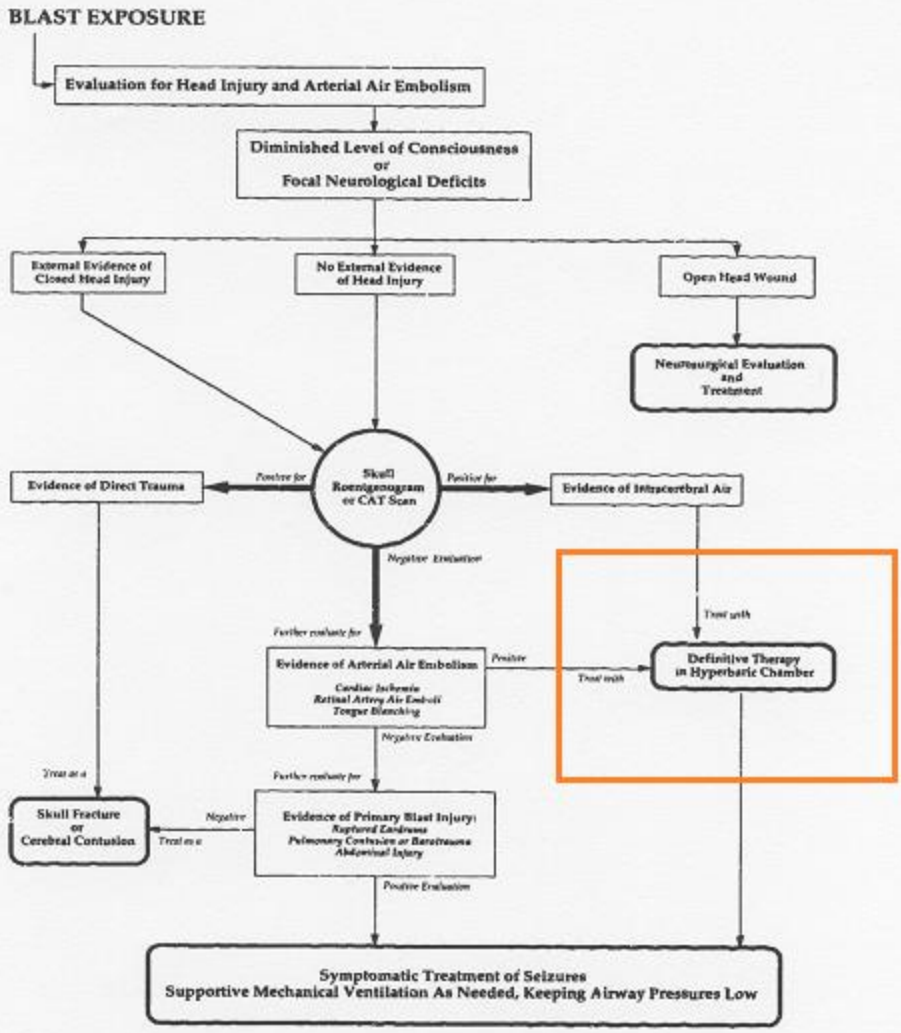


Fig. 9-10 Algorithm for the evaluation of neurological abnormalities in a blast casualty

Textbook of Military Medicine - Series on Combat Casualty Care Part 1 Volume 6 pg 313 Conventional Warfare : Ballistics Blast and Burn Injuries Published by the Office of the Surgeon General Department of the Army, United States of America- Editor in Chief Colonel Russ Zajtchuk, MC U S Army, Deputy Commander, Walter Reed Army Medical Centre . Managing Editor Donald P Jenkins PhD Uniformed Services University of the Health Sciences.
Walter Reed Army Medical Center, Walter Reed Army Institute of Research, Washington DC.
Uniformed Services University of the Health Sciences, Bethesda Maryland.
United States Army Institute for Surgical Research, San Antonio Texas.
Printed in the United States 2006

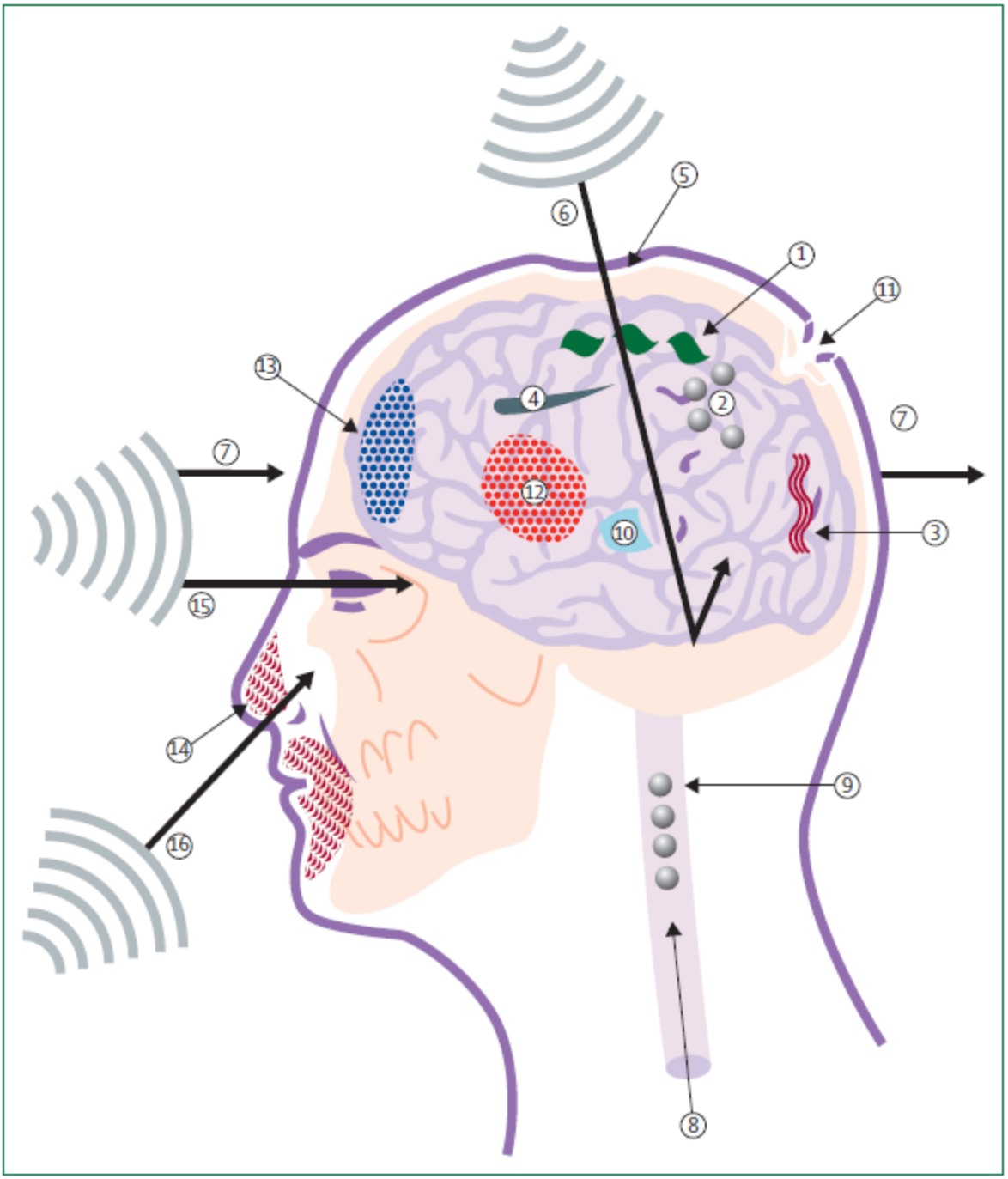


***Figure 1*: Schematic diagram of the mechanisms of blast-related traumatic brain injury**
Figure shows local effects (1–7) and systemic effects (8, 9) of primary blast injury, secondary blast injury (10–12), tertiary blast injury (13), quaternary blast injury (14), and portals for blast wave transmission to the brain (15, 16). (1) Acoustic impedance mismatch causes spallation. (2) Shock–bubble interaction. (3) Shear stress causing diffuse axonal injury. (4) Cavitation. (5) Skull deformation with elastic rebound. (6) Reflection of the blast wave within the skull. (7) Bobblehead effect of acceleration–deceleration. (8) Blood surge from the torso damages the microvasculature. (9) Air embolism from blast lung injury.(10) Penetrating fragments. (11) Compound fractured skull. (12) Intracerebral haemorrhage. (13) Contrecoup contusion. (14) Burns. (15) Blast wave transmitted through the orbits. (16) Blast wave transmitted through the nasal sinuses.

Blast-related traumatic brain injury. Jeffrey V Rosenfeld, et al ***Lancet Neurol*** 2013; 12: 882–93 July 22, 2013 http://dx.doi.org/10.1016/S1474-4422(13)70161-3

15 on-label indications for HBOT are already approved and insured

1. **Air or Gas Embolism****
2. **Carbon Monoxide Poisoning****
   Carbon Monoxide Poisoning Complicated By Cyanide Poisoning
3. **Crush Injury, Compartment Syndrome and Other Acute Traumatic Ischemias****
4. **Decompression Sickness****
5. Arterial Insufficiencies:
   Central Retinal Artery Occlusion**
   Enhancement of Healing In Selected Problem Wounds
6. Clostridial Myositis and Myonecrosis (Gas Gangrene)
7. Severe Anemia
8. Intracranial Abscess
9. Necrotizing Soft Tissue Infections
10. Osteomyelitis (Refractory)
11. Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
12. Compromised Grafts and Flaps
13. Acute Thermal Burn Injury
14. Idiopathic Sudden Sensorineural Hearing Loss (Approved on October 8, 2011 by the UHMS Board of Directors)
15. CMS Covered Condition: Diabetic wounds of the lower extremities in patients who meet the following three criteria [August 30, 2002]

a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
b. Patient has a wound classified as Wagner grade III or higher; and
c. Patient has failed an adequate course of standard wound therapy.

**** These indications are similar to conditions found in brain injury**

TreatNOW

HBOTMechanismsOfAction FEB 2022.pdf
Uploaded by: Robert Beckman
Position: FAV

HBOT:
MECHANISMS OF ACTION

HBOT's mechanisms of action are well known and well characterized both in scientific literature and in clinical practice.

Functional Medicine Methods are Necessary to make these treatments for these conditions ROUTINE!

Typical Monoplace Hyperbaric Chamber

Typical Multiplace Hyperbaric Chamber

Hyperbaric Medicine has been used for 75 years to treat brain insults!

HBOT is approved and on-label for 14 indications and treatment is reimbursed by all major third party payers including Medicare, Tricare and the Veterans Administration.

Hyperbaric oxygen therapy is the only non-hormonal treatment approved by the FDA for biologically repairing and regenerating human tissue.

It is FDA-approved and effective for the treatment of 3 kinds of non-healing wounds.
It is currently FDA-approved as the primary treatment for 3 different kinds of brain injuries: carbon monoxide poisoning, arterial gas embolism, and cerebral decompression sickness.

Hyperbaric Oxygen Therapy is not Black-Labeled by the FDA, as are many drugs currently being prescribed off-label for post-traumatic stress disorder or traumatic brain injury.

FDA Accepted HBOT Indications

HBOT as used by the team is currently in use for 14 FDA-accepted indications (which means the manufacturer or practitioner can advertize those indications) by hundreds of physicians at over 1,000 locations across the nation, delivering approximately 10,000 treatments per day. The fourteen accepted indications for HBOT treatment include:

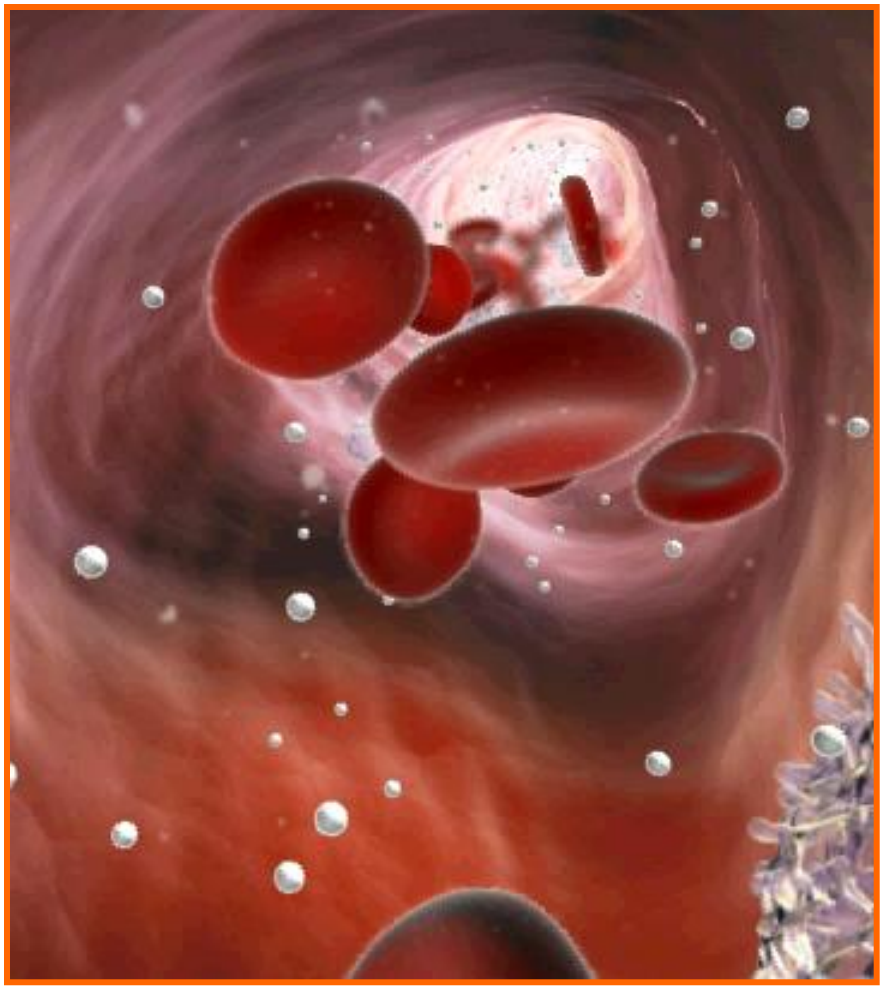
1. Air or gas embolism (results from the bends, rapid decompression and ***Blast Injury***)
2. **CO poisoning, CO poisoning complicated by cyanide poisoning *(Neurological)***
3. Clostridial myositis and myonecrosis (gas gangrene)
4. Crush injury, ***compartment syndrome,*** and other acute traumatic ischemias ***(Non-Healing Wound)***
5. **Decompression sickness *(Neurological)***
6. **Arterial Insufficiency: *(Non-Healing Wound)***

   Enhancement of healing in selected problem wounds (includes uses like Diabetic Foot Wounds, Hypoxic Wounds, and other non-healing wounds, etc.)
7. Exceptional blood loss anemia
8. **Intracranial abscess *(Neurological)***
9. **Necrotizing soft tissue infections**
10. Osteomyelitis (refractory)
11. Radiation tissue damage (soft tissue and bony necrosis) ***(Non-Healing Wound)***
12. **Skin grafts and flaps (compromised) *(Non-Healing Wound)***
13. Thermal burns[1]
14. **Acute Sensorineural Hearing Loss *(Neurological)***

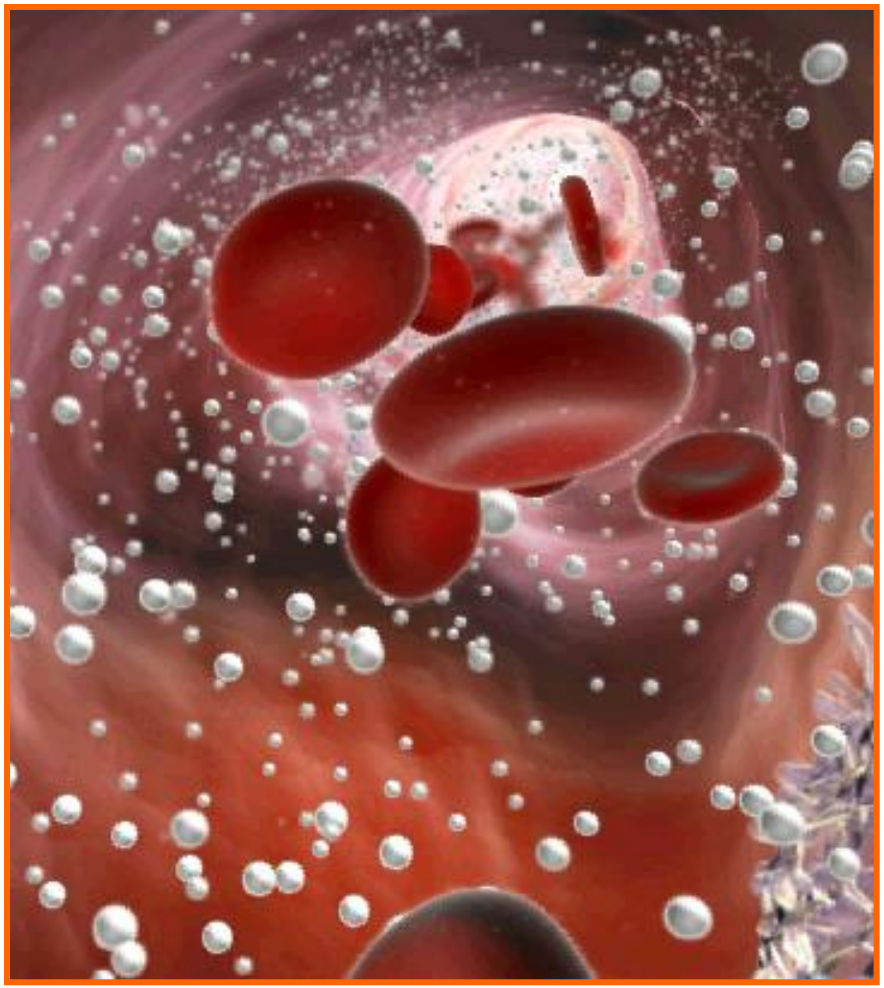
[1] Hyperbaric Oxygen Therapy: 1999 Committee Report. Editor, N.B. Hampson. Undersea and Hyperbaric Medical Society, Kensington, MD. See also: Harch PG. Application of HBOT to acute neurological conditions. Hyperbaric Medicine 1999, The 7th Annual Advanced Symposium. The Adams Mark Hotel, Columbia, South Carolina, April 9-10, 1999; and Mitton C, Hailey D. Health technology assessment and policy decisions on hyperbaric oxygen treatment. Int J of Tech Assess in Health Care, 1999;15(4):661-70.

HBOT: It's About Oxygen Saturation

The body's liquids are saturated with more oxygen, helping areas with compromised circulation.



Before HBOT



After HBOT

Image Courtesy of Dr. Stoller

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Solution: It's Just Oxygen!

HBOT: Oxygen is being used to repair an injury caused by a lack of oxygen!

- **Simple: Lack of oxygen is bad**
- **O2 used in 5,769+ cellular processes**
- **HBOT activates 8,101 Genes!**
  - Down Regulates Inflammation Processes
  - Up Regulates Growth & Repair Processes
  - Normobaric O2 does not!
- **We know how HBOT works!**
  - Acutely stops swelling/reperfusion injury
  - Restarts stunned cellular metabolism
  - Restarts Stunned Mitochondria
    - Mitochondria then Request Oxygen (Blood Supply)
    - Body Re-grows Blood Vessels
  - Activates Stem Cells 8x Normal
    - to repair neural pathways and grow new tissue
- **No wound can heal without oxygen**
  - Wounds that have not healed need more O2
  - Wounds heal 50% faster with less scar tissue
  - Broken bones 30% faster & 30% stronger
- **Placebos have to have the potential of being inert.** Saturating injured tissue with any dose of oxygen has never been shown to have a placebo effect!

Pressure causes oxygen to saturate tissues higher than normal breathing:

HBAT 1.3: 30%* more O2

HBOT 1.5: 700% or 7x

HBOT 2.4: 1200% or 12x

HBAT is Compressed Air & HBAT 1.3 is the FDA Approved Treatment for Mountain Sickness

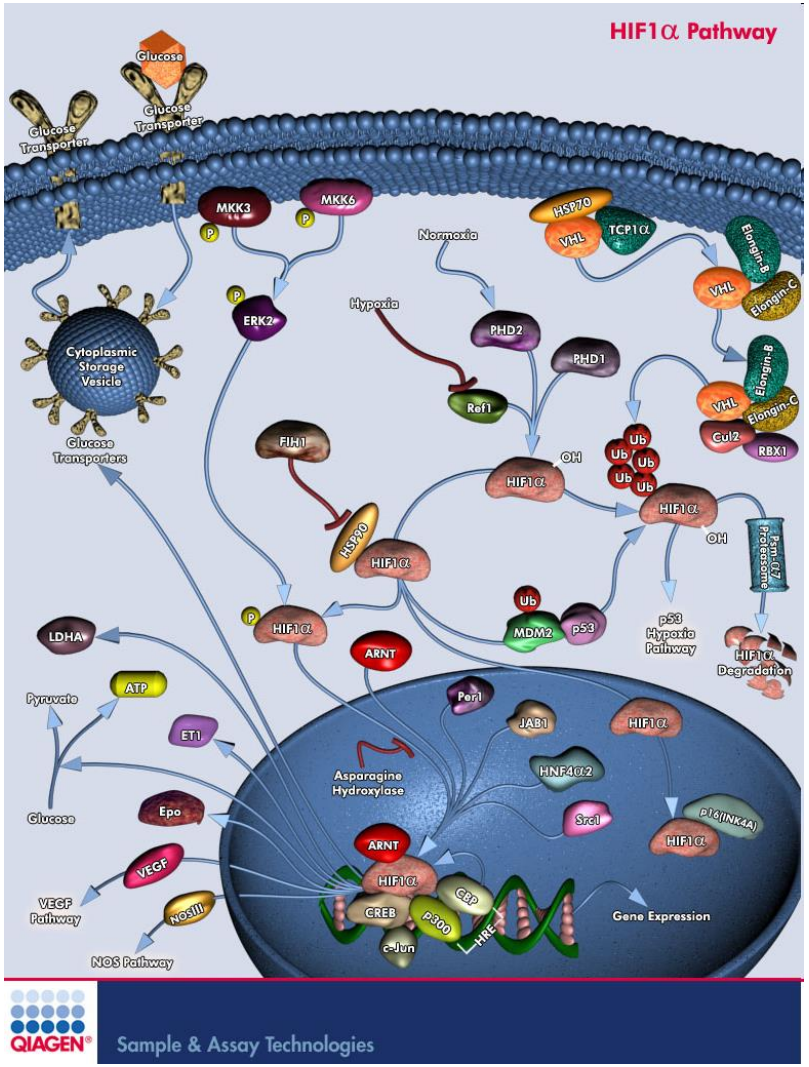
HBOT is FDA-approved & available & On-Label for neurological conditions & non-healing wounds!

*25% more O2 in tissues is so clinically significant that DoD medicine has spent millions in research trying to achieve it. It is already available on the battlefield with mountain sickness chambers using air!

How Oxygen works - 5,769+* ways

(~# of cellular processes studied)

- Upregulates growth factors
- Reduces edema/swelling
- Promotes neural pathway growth
- Activates senescent neurons [“sleeping”, not dead]
- Increases neuronal energy [ATP]
- Downregulates inflammation
- Reduces reperfusion injury [not enough O2]



*Rink C, Roy S, Khan M, Ananth P, Kuppusamy P, Sen CK, Khanna S. Oxygen-sensitive outcomes and gene expression in acute ischemic stroke. J Cereb Blood Flow Metab. 2010 Feb 10.

HBOT: Its about the Mitochondria

Neuroscience 137 (2006) 493–504

OXYGEN-INDUCED MITOCHONDRIAL BIOGENESIS IN THE RAT HIPPOCAMPUS

D. R. GUTSAEVA,[a,b] H. B. SULIMAN,[a]
M. S. CARRAWAY,[a] I. T. DEMCHENKO[a,b] AND
C. A. PIANTADOSI[a]*

[a]*Departments of Medicine and Anesthesiology and Center for Hyperbaric Medicine and Environmental Physiology, Duke University Medical Center, Box 3315, Durham, NC 27710, USA*

[b]*Institute of Evolutionary Physiology and Biochemistry Russian Academy of Science, St. Petersburg, Russia*

1972; Balentine, 1982). The mechanisms of Cl
icity, although not fully understood, involve the
of reactive oxygen and nitrogen species (ROS
that disrupt the brain's oxidant/antioxidant bala
chenko et al., 2002). This imbalance promotes
ecule oxidation, including lipids, enzymes, and
ids, which in theory produces the neurocher
ations and manifestations of toxicity (Jamies
Fridovich, 1998).

Image Courtesy of Dr. Stoller

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HBOT Acts on Mitochondria

Restart Cellular Metabolism

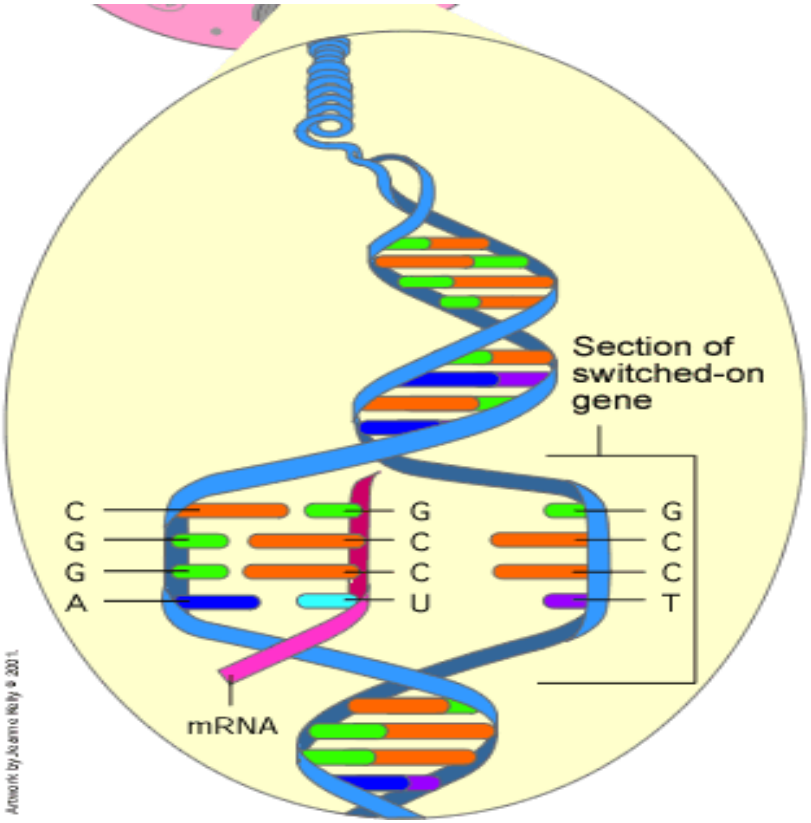
- Brain Death is diagnosed and declared when there is no blood in the brain. - Why?
- **The Brain is not asking for blood.** Why?
- The various cells in the brain are not asking for blood. Why?
- Mitochondria are not asking for Oxygen
- Idling Neuron-Lancet Letter
  - Neurons become Dormant before Death and can be reactivated by saturating body fluids with oxygen
- **Dormant Cells have now been found throughout the body, from hearts to lungs.**

Request for Oxygen Supply

- **Dormant or stunned neuron mitochondria make 2 ATP**
- **HBOT Reactivated 36 ATP are made**
- **When Reactivated, mitochondria immediately begin requesting O2**
- **If O2 is not readily available because the blood supply has been compromised, DNA is signaled to start repair and grow a blood supply.**
- **HBOT-O2s Pulsed Dose in HBOT protocols keep the process going.**
  - **Academic Medical Research has been focused on trying to force the blood supply into damaged areas**
  - **The natural process repairs metabolism inside the cells, which then sends the repair signals out.**

Source: Leo Germin, MD, Neurologist, Las Vegas, Nevada

HBOT works at the DNA level



- Decreases hypoxia-inducible factor-1α (hip-1α) & multiple genes related to apoptosis (programmed cell death)
- Inhibition of apoptosis by HBOT translates into brain wound healing

Zhang, JH et al. Neuroscience and Critical Care Yin, W Brain Res 926: 165-171

Badr et al 2001 brain Res 916: 85-90 Atochin, DN 2000 UHMS 27: 185-190

Image Courtesy of Dr. Stoller

HBOT: It's About Your Own Stem Cells

Stem cell mobilization by hyperbaric oxygen

Stephen R. Thom, Veena M. Bhopale, Omaida C. Velazquez, Lee J. Goldstein, Lynne H. Thom and Donald G. Buerk

Am J Physiol Heart Circ Physiol 290:1378-1386, 2006. First published Nov 18, 2005;
doi:10.1152/ajpheart.00888.2005

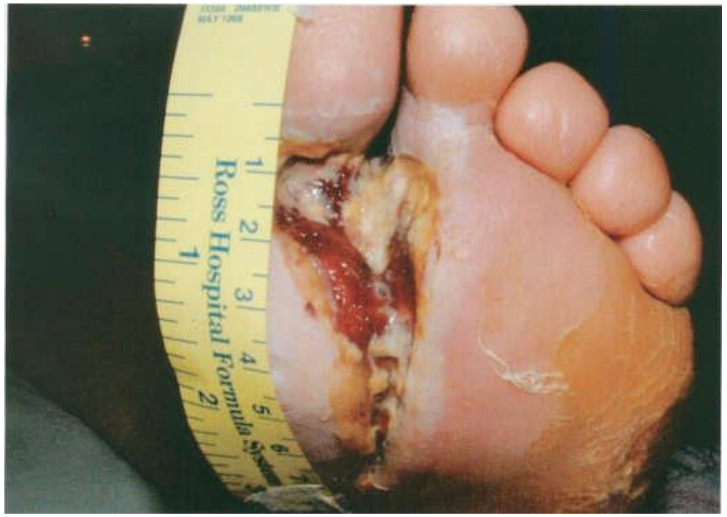
In humans, HBOT at 2.0 atm and 100% oxygen for 2 hours per treatment for 20 treatments increased the number of circulating stem cells in the blood by 8-fold

Thom et al., 2006
Am J Physiol Heart Circ Physiol 290:1378-86

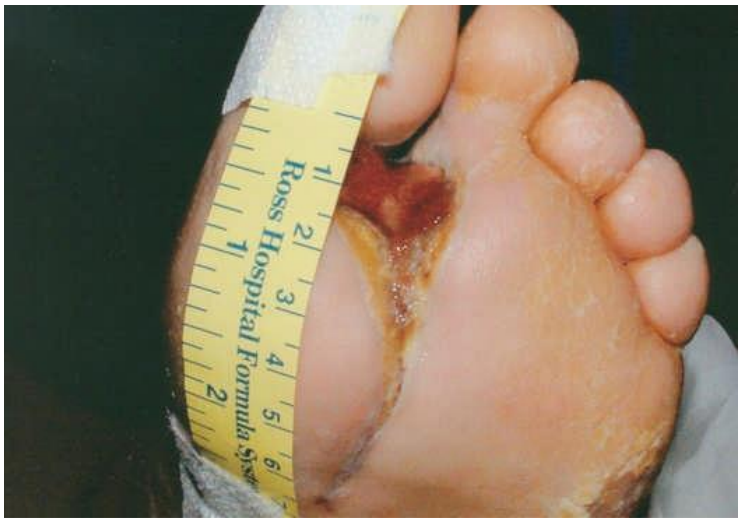
Image Courtesy of Dr. Stoller

Non-Healing Wound of the Foot

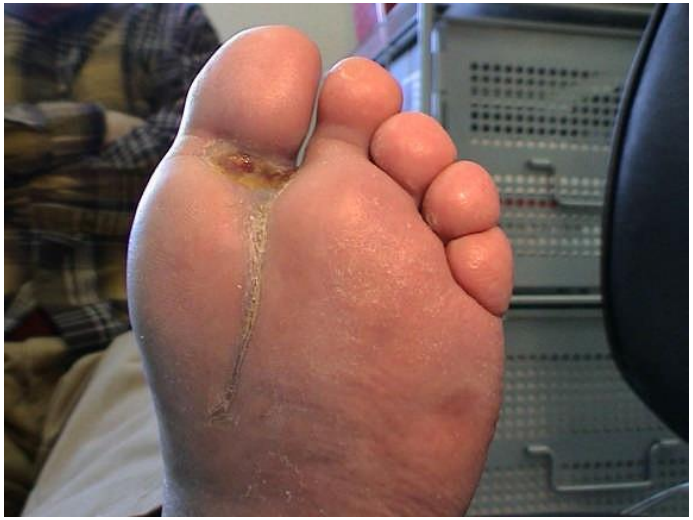
Diabetic Foot Ulcer: This Wagner Grade III was present for one year and unresponsive to conventional therapy.



1 Day Prior to Scheduled Amputation



26 HBOT Treatments



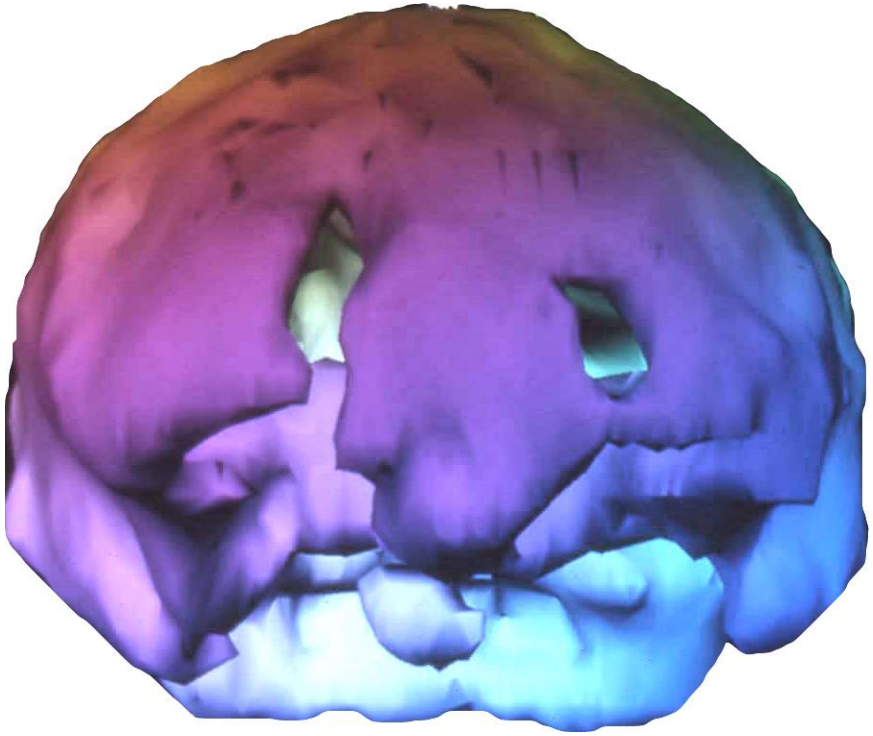
50 HBOT Treatments

Hyperbaric Oxygenation prevents 75% of amputations in diabetic patients. Therapy approved by CMS for Medicare upon application by IHMA to CMS for coverage, 2003.

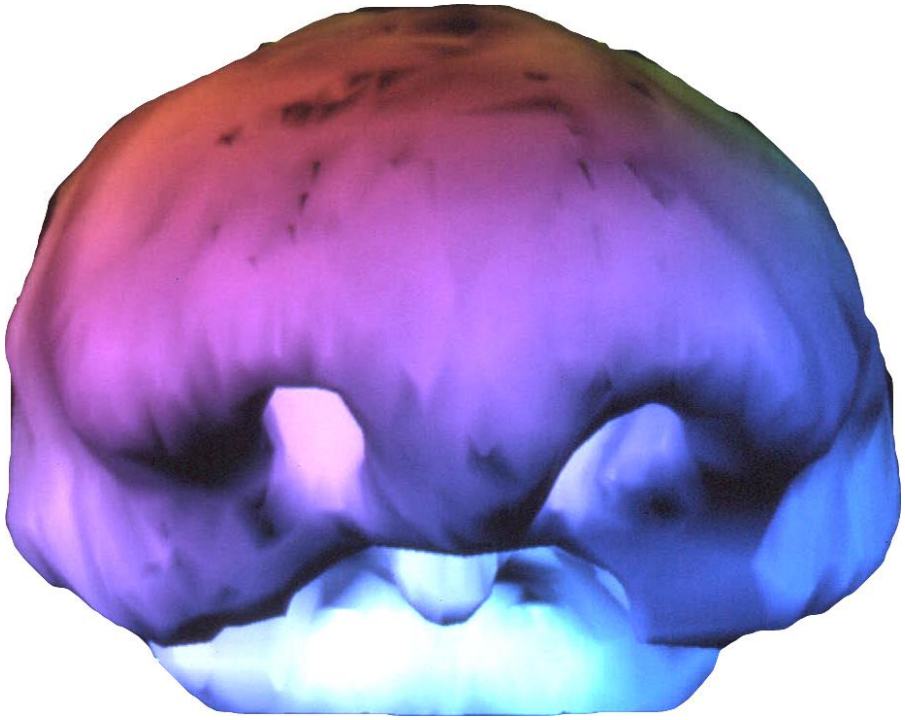
These photographs are the property of Kenneth P. Stoller, MD, FAAP
Permission given by Dr. Stoller to the IHMA to publish on this CD (2004)

Non-Healing Wound of the Brain

Physical Abuse - 9 years after Injury - 21 y. female



Pre-HBOT 1.5



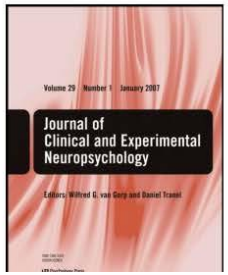
Post-HBOT 1.5

No wound will heal without oxygen!

What is the difference between the diabetic non-healing foot wound and the non-healing brain injury? Essentially nothing. FDA has already approved HBOT for 3 kinds of non-healing wounds and 3 neurological injuries!

Myth: “90% Recover from Brain Injury”

“Recovery” does not mean “healed without residual effect” or restoration to prior mental capabilities.



Journal of Clinical and Experimental Neuropsychology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713657736

Persisting effects of minor head injury observable during hypoxic stress

R. Ewing [a]; D. McCarthy [b]; D. Gronwall [c]; P. Wrightson [c]
[a] Royal New Zealand Air Force Base, Auckland [b] Auckland University, [c] Department of Neurosurgery, Auckland Hospital,

Online Publication Date: 01 October 1980

In conclusion, these results show that simulated altitude with mild hypoxia will cause a significant decrement in the performance of young subjects who have been concussed in the past, when compared with a control group. The decrement resembles that seen immediately after concussion and in old people. The hypothesis proposed in the introduction is, therefore, supported. The most likely explanation of this, and of the cumulative effects of concussion previously demonstrated (Gronwall & Wrightson, 1975), is that concussion produces some persisting deficits in intellectual function, although they may be subtle and only emerge under conditions of stress of further injury.

REFERENCE NOTE

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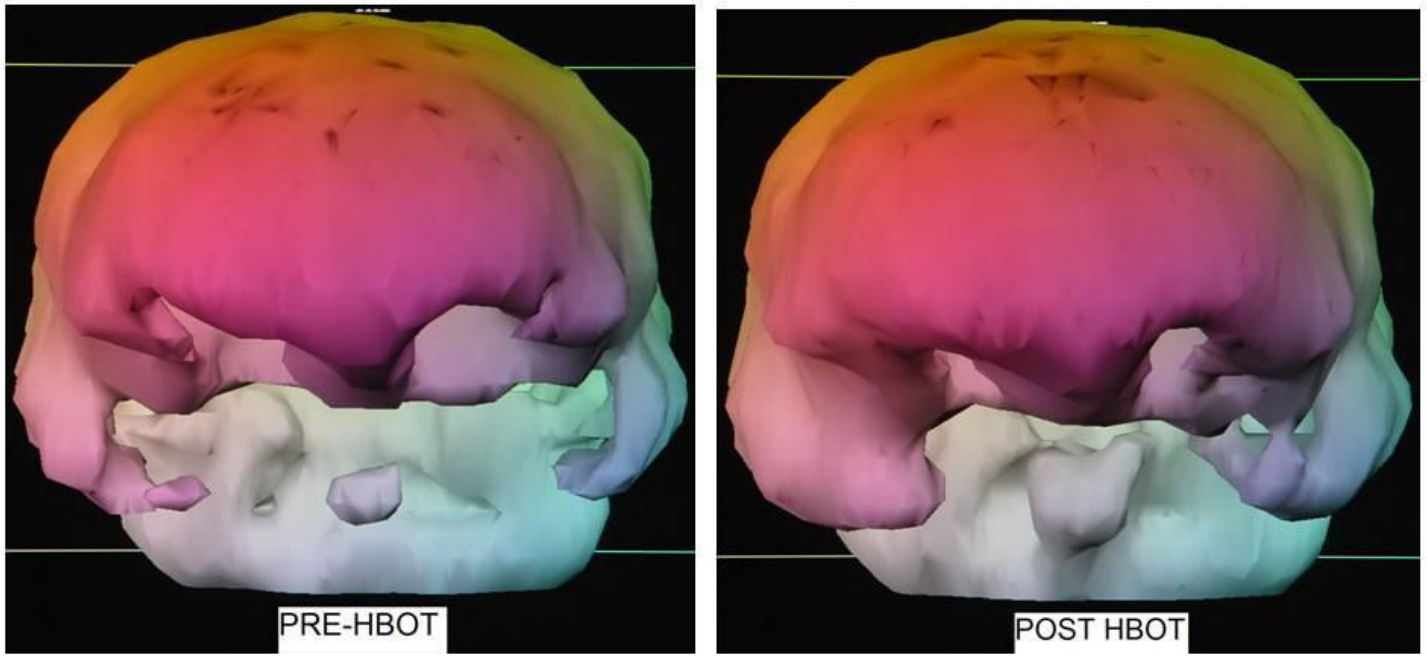
Solution to Brain Injury: Biologically Repair the Brain

Non-Healing Wound in the Brain

Case Report: Navy SG Meeting - Aug. 2008
25 year old Humvee Machine Gunner
40 HBOT 1.5 treatments (1/2 of the Protocol)



Treated in 2008. PTSD disappeared. From living in a dark room since returning from Iraq, he became gainfully employed, turned down ½ of his VA disability, worked and made $39,000 per year, and has returned to college after 2nd 40 treatments.

Case Published in: Cases Report June 2009 http://casesjournal.com/casesjournal/rt/suppFiles/6538/31370

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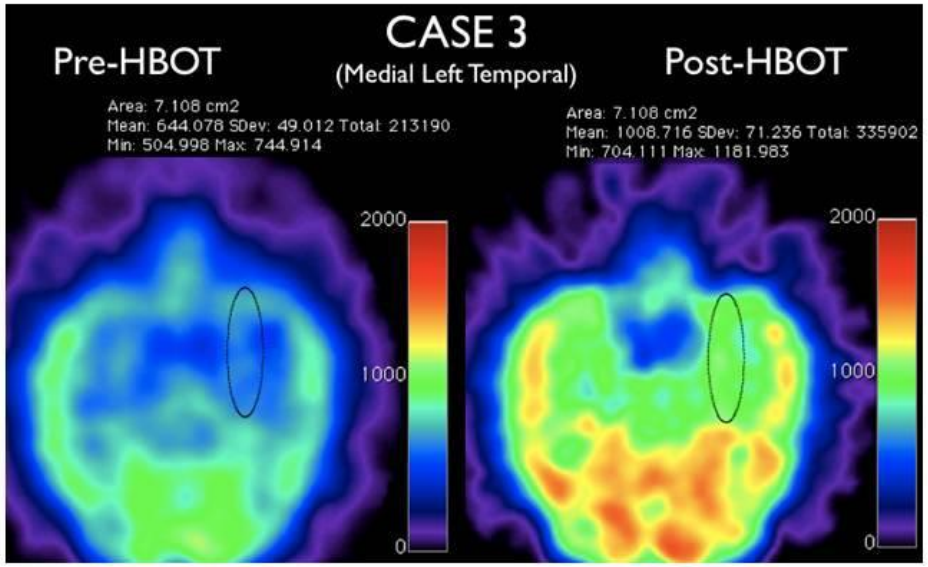
Brain Insults often Result in a 50% Decrease In Brain Metabolism. HBOT Restores Brain Metabolism

HBOT 1.5 Restores Brain Blood Flow & Metabolism

Scale actually goes from 0 to 2000 so it ENDS at 2000. Those pixels that are hitting near 2000 are red and are the most active, the less metabolically active are "cooler" colors of yellow, green and blue. So if you draw a line across the middle of the scale you can see what pixels are registering at 1000 by the corresponding color.

Both pre and post HBOT sets of images are exactly on the same scale. Below is a a quantitative assessment that shows the actually percent increase in up take to an area of the brain quite vulnerable to TBI. Note the mean uptake in the area went from 644 to 1008. Similar changes are evident everywhere else.

In ballpark numbers a change from green to red is a doubling of metabolism.



Analysis of blast injured veteran in LSU IRB Study # 7051: Edward Fogarty, MD, Neuro-radiologist, Chair, University of North Dakota School of Medicine, (701) 751-9579 **40 Treatments: ½ of NBIRR Protocol**

Case Published in: Cases Report June 2009 http://casesjournal.com/casesjournal/rt/suppFiles/6538/31370

The Specific Science for HBOT 1.5

- 1977 Study: Holbach & Wasserman PMID: 75249 : HBOT 1.5 puts the most oxygen into the brain because more triggers an autonomic response to keep extra O2 out! Chronic Stroke patients treated at numerous locations.
- 1990: Harch treats first demented diver for delayed decompression sickness. Numerous small studies published. (See Memorandum)
- 2002: US Army verifies HBOT 1.5 repairs white matter damage in children. ISSN1524-0436
- 2007: Rat HBOT 1.5 study for Chronic TBI published in Brain Research. Human protocol in Animals. First improvement of chronic brain injury in animals in the history of science. PMID: 17869230
- August 14, 2008: Briefing to Surgeon General of the Navy & Deputy Commandant, US Marine Corps: 5 blast injured veterans treated. All five made improvements, some dramatic. Four of five were able to return to duty or civilian employment! First Case was Published April 2009 PMID: 19829822 [PubMed]
- September 2008: US Air Force Hyperbaric Researcher & Special Forces Command Physician treats two airmen. Results verified by ANAM neuropsych test. Both are restored to duty saving the Federal government an estimated $2.6 million each in lifetime costs. They continue their careers. More active duty personnel are treated. Published in January, 2010 in Peer Reviewed Journal (PMID: 20112530) (See Research www.HyperbaricMedicalFoundation.org)
- **March 12, 2010: Report on 15 Blast Injured Veterans under LSU IRB-approved study. Report is clinically and statistically significant and sufficient proof because of dramatic improvement in patients. ½ of protocol given (WBIC0653)**
  - **15 point IQ jump in 30 days p<0.001, 40% improvement in Post-concussion symptoms p=0.002 (np), (10% is considered clinically significant enough to warrant approval and payment for HBOT according to DoD researchers in December 2008.)**
  - **30% reduction in PTSD symptoms p<0.001, 51% Reduction in Depression Indices p<0.001**
- **NBIRR-01 Begins Enrolling Patients March 2010. Preliminary Results from multi-site study support Harch's Findings.**
- **LSU Pilot Published in the Journal of Neurotrauma,** J Neurotrauma. 2011 Oct 25. **A Phase I Study of Low Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post Concussion Syndrome and Post Traumatic Stress Disorder** PMID: 22026588
  - **Subjects as a group showed significant improvements on most measures of intelligence, function and quality of life**
  - **All subjects received 1/2 the clinically recommended protocol being used in NBIRR-01 (NCT01105962)**
  - **Nearly 15 point IQ Increase (average) (Difference between a high school dropout & a college graduate)(14.8 P<.001)**
  - **Post-Concussion Syndrome (PCS): 39% Reduction in PCS symptoms (p=0.0002); 87% substantial headache reduction**
  - **30% Improvement in PTSD (20 points of a 85 point scale; 10% is considered clinically significant)**
  - **51% Reduction in Depression Indices with Large Reduction in Suicide Ideation(p=0.0002)**
  - **64% had a reduced need for psychoactive or narcotic prescription medications**
  - **100% showed sustained improvement on neuropsychological tests 6 months post treatment**
  - **Functional Improvements: Cognitive 39% (p=0.002); Physical 45% (p<0.001); Emotional 96% (p<0.001)**
    - **Significant Reduction in Anger Issues!**
  - **Placebo Effect Ruled Out! Results too great to be placebo effect and neurological imaging is inconsistent with a placebo effect**

HBOT 1.5 Provided the Largest Published Reduction in PTSD

- LSU Pilot Study: 30% Reduction
- Cognitive Processing Therapy [TAU]: 14%↓ or 4.8%↓
  - -Chard, 2011 & Alvarez 2011
- Trauma Focused Group Treatment [TAU]: 2.2%↓
- Prolonged Exposure Therapy [PE]: 28%↓ -Wolf, 2012
- Transcendental Meditation [TM]: 21%↓ -Rosenthal, 2011
- Virtual Reality Exposure Therapy [VRET]: 23%↓
  - Rizzo, 2011

Note: All results are time adjusted for the length of treatment in the LSU study

HBOT is Rapidly Deployable

- **Note the Level of Education needed for health care professional providing treatment in the previous slide.**
  - Subjects in other therapies had a Masters or Ph.D. or Physician level therapist.
- **HBOT can be delivered** by a health care provider with **EMT level 1 or better training**, with overall physician supervision.
- **Thus HBOT is more readily deployable, a lower strain on resources, and more effective than any other published therapy.**

TreatNOW Is Solving the TBI/PTSD Problem

- The Challenge is Getting Paid for Treatment So We can Restore People's lives!
  - State Medicaid Rules Restrict Treatment Locations
  - Payment is NOT made even when patients recover!
- No Other Such Clinic Treatment Network Exists!
- Our Team Leaders have decades of experience with Hyperbaric Medicine
  - Our Team Leaders have over 20 years of experience treating Brain Injury & restoring lives with this protocol
- **TODAY the TreatNOW Coalition is Helping Solve the Real Problems of Brain Injured Persons with Biological Repair for their brain wounds, the "invisible wounds" of war**

Airman B ANAM Percentile Scores

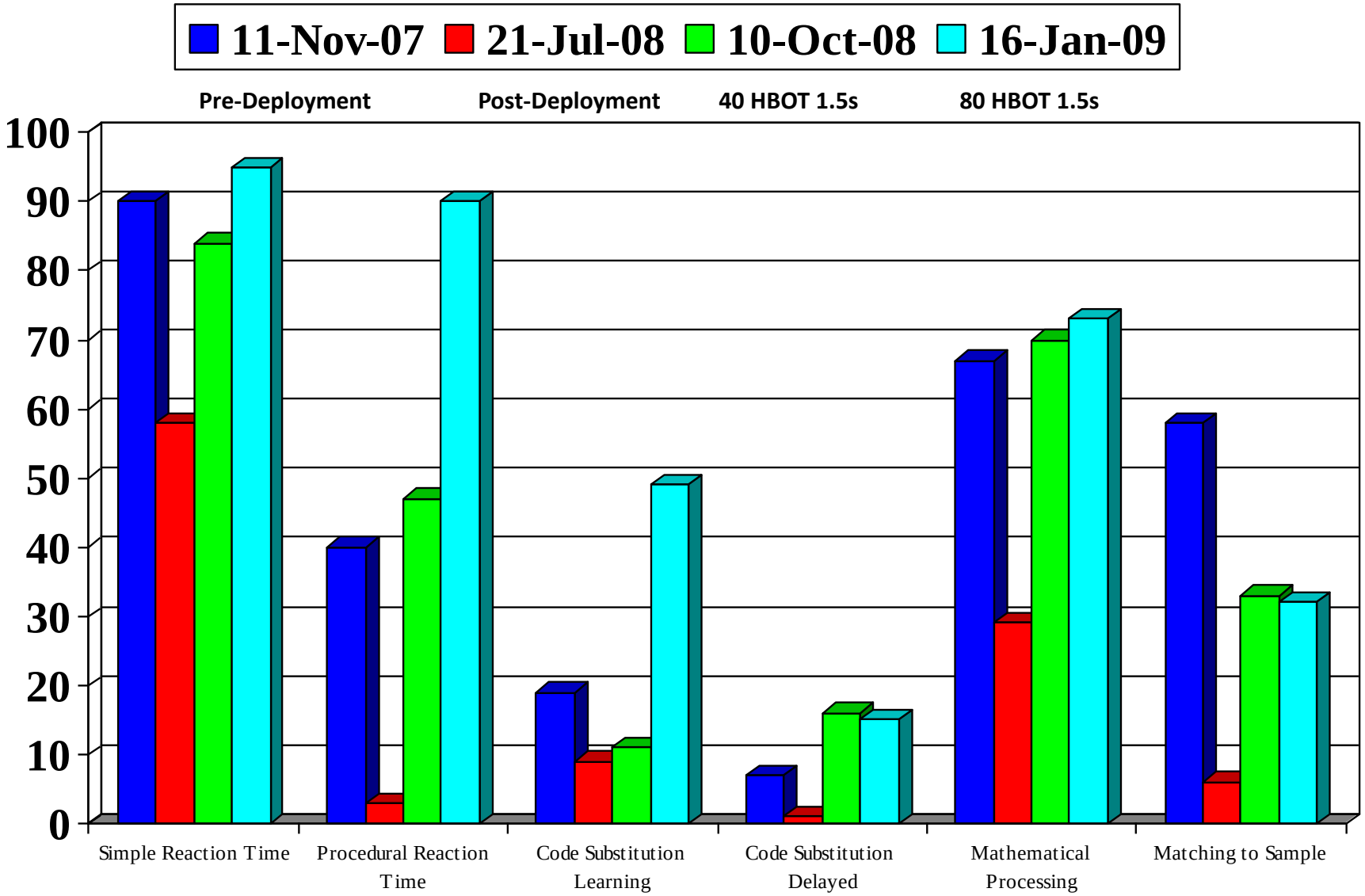


Figure 1:
The passenger side of the M915 truck showing the damage caused by the IED.

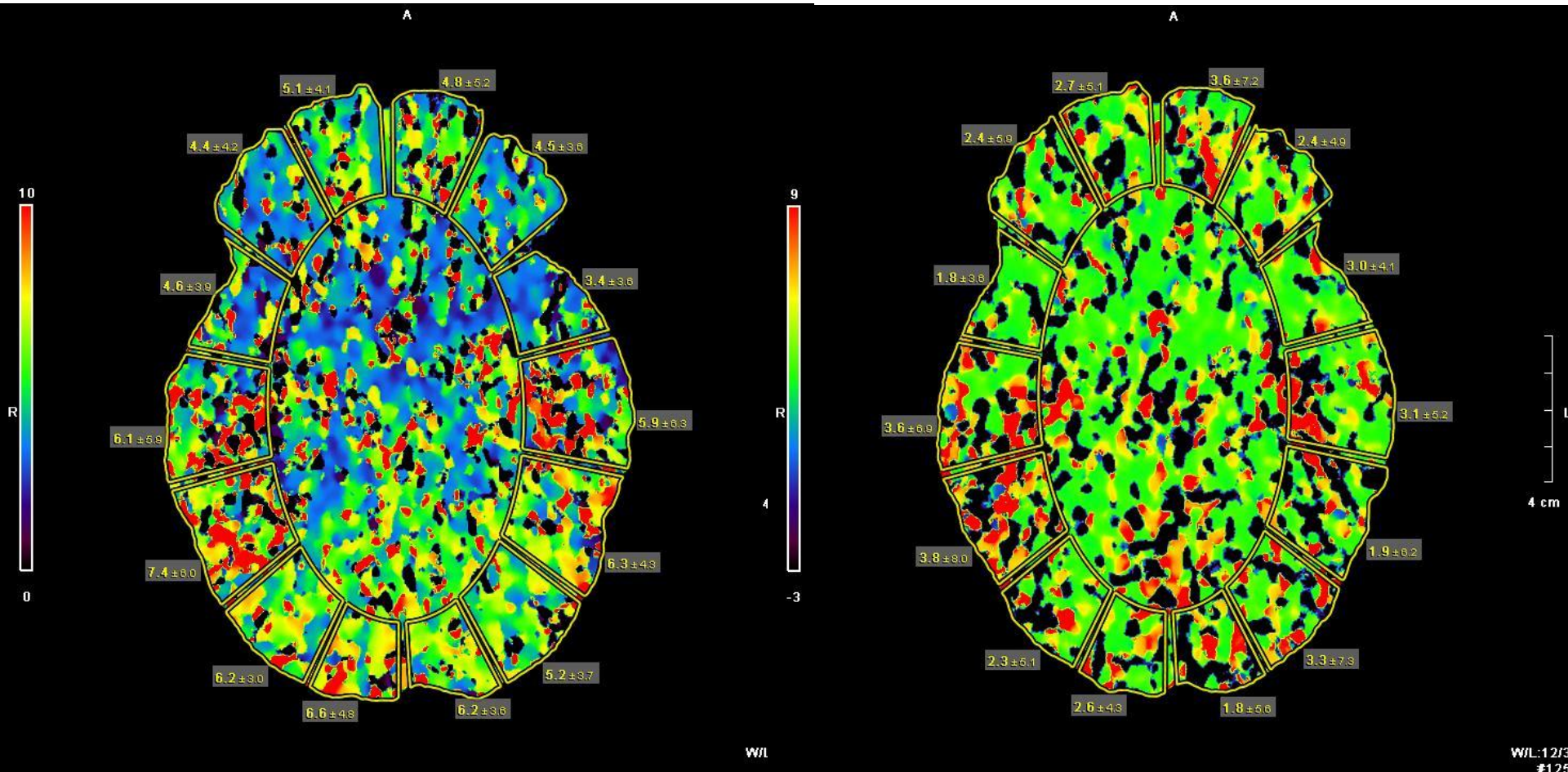
Conclusion by article authors:

Several aspects of these two cases demonstrate the efficacy of HBO for the airmen treated. Although both airmen had stable symptoms of mTBI/post-concussive syndrome, which had not improved for seven months; **substantive improvement was achieved within ten days of HBO treatment. The headaches and sleep disturbances improved rapidly while the irritability, cognitive defects, and memory difficulties improved more slowly.**

Fortunately both airman had taken the ANAM and presented objective demonstration of their deficits from TBI and their improvements after HBO treatment. Both airmen, who were injured by the same blast sitting side by side, had similar symptom complexes of TBI and improved at similar rates after initiation of HBO treatment. Neither airman had any other form of treatment for TBI. **It seems unlikely to the authors that any explanation other than the HBO treatments can be offered for their improvements.**

"Case report: Treatment of Mild Traumatic Brain Injury with Hyperbaric Oxygen: Colonel James K. Wright, USAF, MC, SFS; Eddie Zant, MD; Kevin Groom, PhD; Robert E. Schlegel, PhD, PE; Kirby Gilliland, PhD"

Severe TBI Patient: Whole Brain CT Perfusion Pre & Post HBOT



Pre HBOT – 10/16/09 Post HBOT – 10/28/09

Images Courtesy of Dr. Germin, Las Vegas

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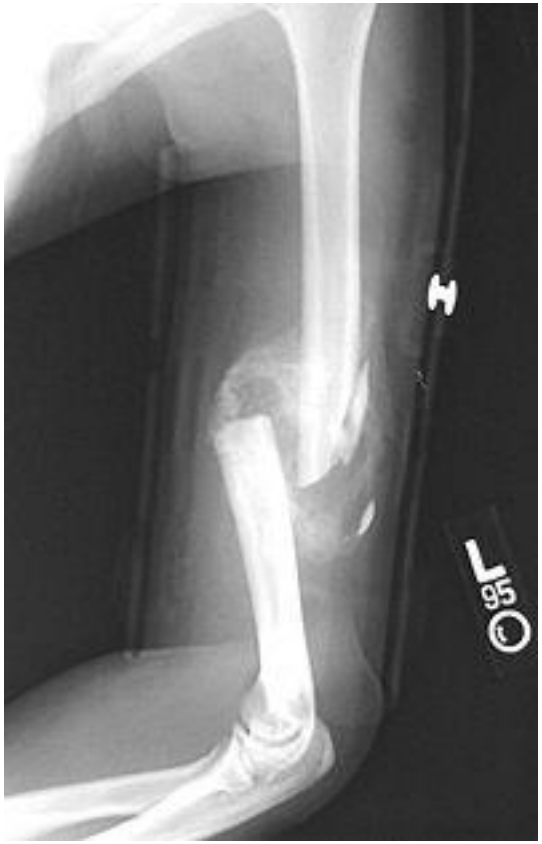
Heal Brains. Restore Lives.

Fractures



- **Dr. Wright's Air Force Research Demonstrated that Fractures heal 30% faster and 30% stronger when Hyperbaric Oxygen is used.**
  - Shorter back to work time
  - Stronger Fusion
- Cost Effective through reduced down time

The effect of hyperbaric oxygen on fracture healing in rabbits, completed 2003. J Wright

Is Hyperbaric Medicine Safe?

Source: "HBOT for TBI" Consensus Conference, December 2008

- **Treatment involves simply breathing pure oxygen under pressure** (often while sleeping or watching TV).
- **Ten thousand plus similar treatments are given every day at 1,200+ locations nationwide for other indications.**

- The DoD White Paper stated: **"side effects are uncommon and severe or permanent complications are rare…"** *(White Paper for the HBOT in TBI Consensus Paper, 12/08)*
- The DoD After Action Report stated: **"safety of the treatment is not an issue."** *(After Action Report HBOT in TBI Consensus Conference, Defense Centers of Excellence, 16 Dec 2008)*

Examples: HBOT is Synergistic with Other Treatments

- Drug Protocols
  - Patients in the LSU Study were on no medication or less medication
  - Medication was now more effective at controlling remaining symptoms
- Nutritional Programs
  - NBIRR Nutritional Program reduced Aberrant Violent Behavior in Felons in 30 RCT Studies by 39-41%
  - Harch did not use NBIRR supplement in his study
- Cognitive Rehabilitation
  - Treatment Cannot Begin until a Patient can Sleep Through the Night
  - HBOT Repairs Sleep Cycles and most Patients can begin sleeping at 10 HBOT Treatments
  - When Brain Tissue is Recovered, it is somewhat disorganized!
- Acupuncture
- Bio-Feedback
- Counseling & Coping Skills

Micro Air Embolism Contribution to Blast-Induced Mild Traumatic Brain Injury

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INTRODUCTION

Massive air embolism (AE) from lung disruption is the accepted principal etiology of mortality in blast injury (White et al., 1971; Sharpnack, Johnson & Phillips, 1990). For sub-lethal blast injury, air embolism has been ignored, considered innocuous or believed to have not occurred. The high incidence of post-concussion syndrome (PCS), neurocognitive deficits, and mental health issues resulting from sub-lethal blast injuries in U.S. Iraq and Afghanistan War veterans has vexed military authorities and medical specialists. We propose that micro air embolism is a heretofore unappreciated etiologic factor.

MATERIALS AND METHODS

Materials and Methods: Using PubMed, PsychInfo, Google Scholar, Sci.gov, and PubCrawler, a systematic review of the literature was conducted identifying published papers in the following domains: biodynamics and physics of blast overpressure; primary blast injury; microbubbles in systemic circulation from diving and iatrogenic causes; neurological problems and microbubbles. When necessary, key documents were obtained from U.S. Government archives. Reference lists of articles were also scanned. Papers with both significant and null findings were included.

RESULTS

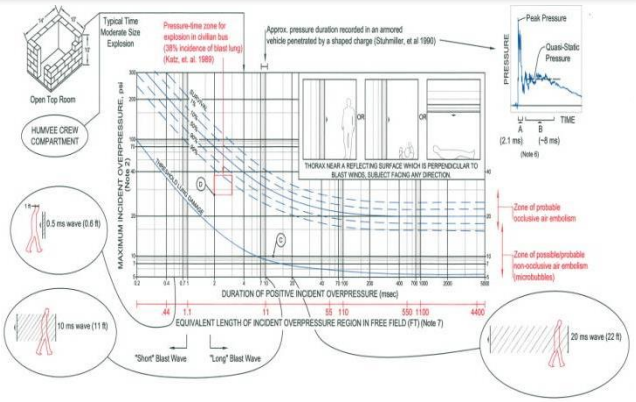
Blast-induced AE

- For mammals that die promptly from either air or underwater blast, air embolism has long been recognized as the primary cause of death (Desaga,1950; Shapnack, Johnson & Phillips, 1990; Richmond & Damon, 1991). Lung disruption is proportional to both magnitude and length of blast overpressurization (Buamoul, 2009) with disruption beginning to occur at modest overpressures easily within the range of pressures experienced by U.S. combat troops from improvised explosive devices (IED) (Fig 1 & 3).
- The disruption threshold is lowered by exposures near reflective surfaces, exposures inside structures that impede dispersion of the blast gases, and by longer exposure times. It is further lowered by repeat exposures in less than 24 hours (Stuhmiller, Phillips & Richmond, 1990).
- Benzinger (1950) concluded that because symptoms were only present when a blast hit the thorax, air embolism must originate in the thorax and becomes effective when it travels to the brain. Benzinger also found that small amounts of air in arterial circulation could readily reproduce neurologic symptoms seen in blast injury to dogs and humans. Only 1 cc of air injected into the pulmonary veins of a dog was sufficient to reproduce the electrocardiographic changes seen in blast-injured dogs (Phillips & Richmond, 1990).
- Maison (1971) outfitted a dog with a Doppler bubble detector on the carotid artery, exposed the dog to an LD50 air blast, and subsequently observed bursts of Doppler deflections going up the carotid correlating with respirations for approximately 30 minutes post-blast. The dog's carotid blood flow was observed to temporarily drop to near zero following each group of echoes, possibly indicating reduced blood velocity due to temporary distal occlusions (Fig. 2). The dog initially showed severe respiratory distress, but recovered. Postmortem exam showed evidence of residual lung hemorrhage, but no other damage. Maison concluded that the bubbles were "clinically silent".
- A conceptual model of how AE sequelae to blast exposure occurs, confirmed with rabbit model data, can be found in White (1971). Any fast-rising blast pressure wave long enough to produce significant chest compression is likely to produce some AE.
- Goh (2009) and Mayo & Kleger (2006) in separate articles regarding civilian blast casualty management advise that AE is a possible complication of exposure to air blast. However, neither author addresses the possibility of neurocognitive sequelae from AE.
- Protective vests reduced mortality & neural fiber degeneration in rats exposed to air blast (Long, et.al., 2009)

Evidence that microbubbles are NOT harmless

- Microbubbles were first recognized as a medical hazard in open-heart surgery decades ago (Barak & Katz 2005). Air emboli from various sources in the extracorporeal circulation (ECC) set and tubes can drift into the aorta and systemic circulation, carrying microbubbles to the brain. Clinical results of this unwanted event include major and minor neurologic injury, neurocognitive deterioration and an overall general decline in patient health (Barak, Nakhoul & Katz, 2008; Shaw et al., 1987). The degree of decline in cognitive performance has been correlated to the amount of air emboli delivered during the ECC (Deklunder et al., 1998[1,2]). Patients with neuropsychological deficits 5 to 7 days after coronary bypass graft surgery averaged nearly twice the number of emboli compared to those without deficits (Stump, et al., 1996).
- In mechanical heart valve carriers, bubbles are chronically delivered into the arterial system at variable rates, which can rise as high as 800 per hour in the cerebral circulation. Patients with these devices have been found to have impairment in episodic memory and deficits in working memory (Deklunder et al., 1998[1,2]).
- Multiple brain lesions in divers with no reported history of neurological DCS have been found to be strongly correlated with patent foramen ovale of high haemodynamic relevance. This finding lead the authors to a hypothesis that the brain lesions were the consequence of subclinical cerebral gas embolism (Knauth et al., 1997).
- A review of 140 cases of delayed DCS treatment (avg. delay 93.5 hrs) reported findings of neurocognitive symptoms including severely reduced executive function, apathy and antisocial behavior in 49% of the patients. 100% of the neurocognitive symptoms resolved with hyperbaric oxygen therapy (HBOT) (Cianci & Slade, 2006).

Fig. 1: Blast Waves Are More Than Simple Shock Waves, Duration Makes a Difference



Notes to Fig. 1

1.Figure is based on the survival curves for a 70 kg man where the thorax is near a surface against which a blast wave reflects at normal incidence (Bowen, Fletcher, & Richmond,1968). data shown is for a single reflection where the total overpressure is ~2x incident pressure. Total pressures can be up to 8x incident pressure if circumstances are right (Richmond & Damon,1991). In free field exposures (no reflections) the damage thresholds are approx. 2x those shown. When used, free field pressure data values are plotted at 50% of actual.

2. "Short" and "Long" refer to the ratio of the length of the overpressure region to thorax dimensions. Long blast waves produce much greater chest compression (White et al., 1971).

3. Repeat exposures in less than 24 hours, lower the lung damage threshold (Stuhmiller, Phillips & Richmond 1990).

4.The lung damage threshold curve is based on an estimated damage threshold of 20% of the 50% mortality level (White et al., 1971). Recent data (Yang et al., 1996) suggests the threshold pressures for lung damage may be lower (circa 50%) than those shown.

5.Blast waveform is also important. However, that is beyond what can be addressed in this poster. a wave speed of Mach 1. Most blast waves are faster (up to Mach 2+) increasing the wave length for the same time..

6.A = shock wave period, B= period where expanding blast gases maintain compartment pressure

7. Based on

Fig. 2 Blood Velocity & Embolus Indications Following Canine Exposure to LD50 Air Blast

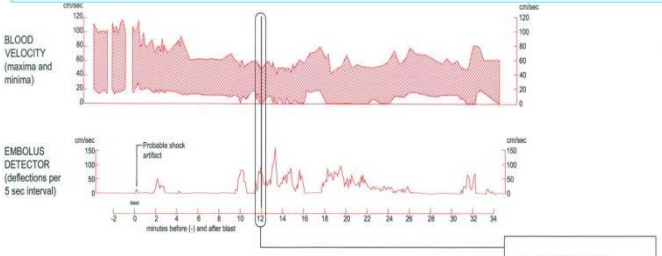
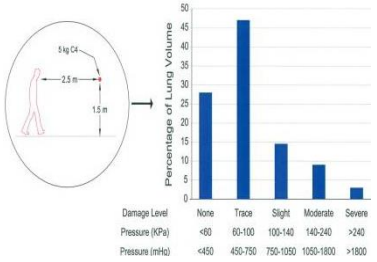


Fig. 3 . Lung Injury Prediction from CRDC Model



Notes to Fig 3.

1. Data shown are peak intro-thoracic pressures and lung damage estimates for a complex (2-peak) wave with a total impulse considered "threshold" for lung damage in a free field (Point D in Fig. 1)
2. Data from Yang, et.al (1996) suggests the threshold for "Trace" damage may be significantly lower that assumed by the CRDC model.

RESULTS (CON'D)

- In hemodialysis, CNS abnormalities attributed to microbubbles have been correlated with the duration of dialysis treatment. Barak & Katz (2008) attributed the abnormalities to microbubbles and stated "a small quantity of microbubbles may be clinically silent, while recurrent exposure has a slow, smoldering, chronic effect" (p. 2921)

Recent Combat Medical Literature

- Bauman et al. (2009) provides a summary of the test conditions and initial results from the PREVENT (Preventing Violent Explosive Neurotrauma) research program being conducted by DARPA. In the tests reported (swine model), the thorax and upper abdomen were protected to minimize the possibility of brain injury by indirect pathways. Some neurological damage was observed, and its significance is still being determined. However, the test conditions are of interest as they are also ones where lung injury can readily occur. Point C on Fig. 1 represents a typical Friedlander wave reported for the blast tube. Test set-ups were built to simulate exposures in the crew compartment of a Humvee with a blast under its floor and an open gunner port and in semi-confined space (open top room with dimensions as shown in Fig 1). In both cases the overpressure durations from a moderate sized charge were reported to be about 4 ms. The overpressure data was reported in general form only without numerical values. However, at 4 ms duration, the pressures required to produce lung injury are not large. In situations where the Humvee or building were to be fully closed, both the magnitude and duration of blast overpressures can be expected to be greater.
- Buamoul (2009) reports results from a computer model developed by Defence R & D Canada (CRDC) for estimating the blast damage to the lungs of sheep and humans. He reports the intra-thoracic pressure range currently accepted as the "threshold" for lung damage is 70 kPa (695 cmH20) to 110 kPa (1,091 cmH20), which corresponds roughly to the intra-thoracic pressures predicted by the model at exposures near the lung damage threshold line on the Bowen charts. The intra-thoracic pressures produced by even moderate size blasts can be very substantial (Fig. 3). They also vary widely with both time and location in the lung, suggesting that opportunities for localized AE may be plentiful. The model also indicates that complex (multi-peak) blast waves can produce higher lung pressures, and therefore greater risk of lung damage than do single peak, classic Friedlander waves of the same impulse value.
- **Recent work by Yang et al.,1996 (sheep model) suggests the lung damage threshold pressure may be as much as 75% lower than the Bowen charts (Fig 1) indicate when the threshold pressure is taken as the lowest pressure at which lung tissue damage is observable by light and/or electron microscopy.**
- It is well established that AE is a possible/probable sequelae of exposure to air blast.
- It is also well established that microbubbles are harmful to brains, and that symptoms may not manifest immediately.
- Blast overpressure exposures typical of the current wars in Iraq and Afghanistan, particularly blast exposures in confined spaces, are sufficient to create risk of lung damage. Quickly repeated exposures increase the risk.
- It is reasonable to expect that the degree of blast-related AE is a continuum ranging from no bubbles, to a few microbubbles to massive amounts depending on the exposure.
- The blast-related intra-thoracic pressures can be very substantial (Fig 3). The range customarily accepted as the threshold for lung injury is 7 to 11 times higher than the 80 mmHg (10.7 kPa) differential known to produce disruption of aveolar-capilary boundary tissues in slowly varying pressure environments such as diving (Neuman, 1997).
- Work by Yang, et. al (1996) suggests that lung tissue damage, and the concurrent possibility of transient microbubble release, can occur at lung damage levels insufficient to produce clinical blast lung and at overpressures substantially lower than indicated by the widely-used Bowen charts.
- The CRDC model confirms suggestions from prior efforts that complex blast waves typical of confined space exposures are more likely to be damaging to lungs than are the simpler waveforms typical of free-field blasts.
- Blast related bubble production, when it does occur, has been shown to be transient, lasting only 15 minutes to 3 hours for significant AE (Mayo & Kluger, 1996). The duration of microbubble production can be expected to be shorter still making them hard to detect.
- All recent publications that we found, including a recent review article (Cernak & Noble, 2009), were silent on the possible role of microbubbles as a mechanism for blast-related brain injury.
- When all the factors that may favor microbubble production are considered, it is difficult to expect they do not occur.
- Undetected arterial microbubbles have the potential to significantly confound research into other mechanisms of blast-related brain injury. **In research studies where there is a possibility of microbubble production, monitoring for their occurrence is recommended**.

The contribution of micro air embolism to blast-related brain injury may be significantly greater than has been previously believed.

Available literature suggests that transient AE from primary blast exposure is possible, perhaps probable, at sub-lethal overpressures similar to the overpressures experienced by U.S. combat Veterans. Arterial microbubbles have been shown to be neurologically harmful and may contribute to the high incidence of post-concussion syndrome in blast injured veterans. Current research efforts are almost exclusively focused on the direct cerebral effects of blast waves. The AE pathway deserves prompt and thorough investigation.

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Types of Hyperbaric Chambers

Monoplace and Multi-Place Hyperbaric Chambers

Sechrist

SOS Hyperlite

Perry

ETC Bara-med XD

Multiplace chambers

Reimers Q-Ball

Israel PTSD.pdf
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PLOS ONE

RESEARCH ARTICLE

Hyperbaric oxygen therapy improves symptoms, brain's microstructure and functionality in veterans with treatment resistant post-traumatic stress disorder: A prospective, randomized, controlled trial

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Abstract

Introduction

Post-traumatic stress disorder (PTSD) is characterized by changes in both brain activity and microstructural integrity. Cumulative evidence demonstrates that hyperbaric oxygen therapy (HBOT) induces neuroplasticity and case-series studies indicate its potentially positive effects on PTSD. The aim of the study was to evaluate HBOT's effect in veterans with treatment resistant PTSD.

Methods

Veterans with treatment resistant PTSD were 1:1 randomized to HBOT or control groups. All other brain pathologies served as exclusion criteria. Outcome measures included clinician-administered PTSD scale-V (CAPS-V) questionnaires, brief symptom inventory (BSI), BECK depression inventory (BDI), brain microstructural integrity evaluated by MRI diffuse tensor imaging sequence (DTI), and brain function was evaluated by an n-back task using functional MRI (fMRI). The treatment group underwent sixty daily hyperbaric sessions. No interventions were performed in the control group.

Results

Thirty-five veterans were randomized to HBOT (N = 18) or control (n = 17) and 29 completed the protocol. Following HBOT, there was a significant improvement in CAPS-V scores and no change in the control (F = 30.57, P<0.0001, Net effect size = 1.64). Significant improvements were also demonstrated in BSI and BDI scores (F = 5.72, P = 0.024 Net effect size =

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: The study was funded by the Research Fund of Shamir Medical Center, Israel.

Competing interests: AH and ES works for AVIV scientific. SE is a shareholder in AVIV scientific.

0.89, and F = 7.65, P = 0.01, Net effect size = 1.03). Improved brain activity was seen in fMRI in the left dorsolateral prefrontal, middle temporal gyri, both thalami, left hippocampus and left insula. The DTI showed significant increases in fractional anisotropy in the fronto-limbic white-matter, genu of the corpus callosum and fornix.

Conclusions

HBOT improved symptoms, brain microstructure and functionality in veterans with treatment resistant PTSD.

Introduction

Post-traumatic stress disorder (PTSD) is a complex, chronic, and debilitating psychiatric disorder that develops in response to severe psychological traumatic exposure. PTSD is characterized by intrusive thoughts, nightmares and flashbacks of past traumatic events, avoidance of trauma reminders, hypervigilance, sleep disturbances and persisting dysregulation of the stress response [1]. These protracted symptoms lead to considerable social, occupational, and interpersonal dysfunctions. The global cross-national lifetime prevalence of PTSD reported by the World Health Organization (WHO) is 3.9% [2], while among combatants the prevalence can be as high as 30% [3]. Unfortunately, the current available treatments, including medications and trauma focused psychotherapy, have limited effect and nearly half of the patients suffer from treatment resistant PTSD [4].

New brain imaging techniques enable better understanding of the pathophysiology responsible for developing PTSD. It is now clear that traumatic events cause long-term changes of brain activity and microstructural integrity. The dominant trauma-related pathologies are demonstrated in the frontal-limbic circuit, amygdala, hippocampus and prefrontal cortex [5–8].

Hyperbaric oxygen therapy (HBOT) includes the inhalation of 100% oxygen at pressures exceeding 1 atmosphere absolute (ATA), thus enhancing the amount of oxygen dissolved in the body tissues. Many of the beneficial effects of HBOT can be explained by improvements in tissue/cerebral oxygenation. However, it is currently understood that the combined action of intermittent hyperoxia and hyperbaric pressure, triggers both oxygen and pressure sensitive genes [9]. Additionally, increases in cerebral metabolic rates, restoration of mitochondrial functions, stimulation of cell proliferation and maturation of endogenous neural stem cells, and induction of anti-inflammatory, angiogenic and neurogenic factors have all been demonstrated after HBOT(9). Cumulative evidence from post-stroke and traumatic brain injury (TBI) studies demonstrate that HBOT induces neuroplasticity in the chronic metabolic dysfunctional brain regions even years after the brain insult [10,11]. Recent studies have also demonstrated HBOT induced neuroplasticity and significant clinical improvements in patients with fibromyalgia, including those in whom fibromyalgia was induced by child abuse [12,13].

The potential beneficial effects of HBOT on PTSD were investigated in combat veterans with TBI which is commonly combined with PTSD. In most of the studies, a significant clinical improvement in PTSD symptoms was demonstrated [14–20]. However, to the best of our knowledge, none of these studies focused on PTSD as a stand-alone pathology.

The aim of this study was to evaluate the effect of HBOT on clinical outcomes, brain functionality and brain microstructural integrity in veterans suffering from treatment resistant combat associated PTSD.

Materials and methods

Study design and patients

The study was a randomized, prospective controlled trial conducted at the Sagol Center for Hyperbaric Medicine and Research at the Shamir Medical Center, Israel, between March 2018 and October 2019. The protocol was approved by the Shamir Institutional Review Board (199/17) and registered in the National Institute of Health Clinical Trials Registry (NCT03466554).

Patients were referred to the study by their psychiatrist or psychotherapist, or applied for the study after reading an advertisement in their veterans' social media groups. The study included male veterans, age 25 to 60 years old, with combat associated, treatment resistant PTSD lasting at least four years prior to their inclusion. Patients were recruited if they had persistent residual debilitating PTSD symptoms, were exposed to at least one trauma focused therapy and pharmacotherapy, and fulfilled the CAPS questionnaire diagnostic criteria for PTSD. Exclusion criteria included history of TBI or any other brain pathology, active malignancy, substance use at baseline (except for prescribed cannabis, and only if nebulized or taken as a tincture), current manic or psychotic episodes, serious current suicidal ideation, severe or unstable physical disorders or major cognitive deficits at baseline, HBOT for any reason prior to study enrollment, chest pathology incompatible with pressure changes (including active asthma), ear or sinus pathologies incompatible with pressure changes, inability to perform an awake brain MRI and active smoking.

Cognitive evaluation at baseline was performed using the computerized cognitive testing battery "Neurotrax". Cognitive scores are presented as normalized scores according to age and education groups, on an IQ-style scale, where 100 is the mean normalized score and one standard deviation equals to 15 points [21].

Randomization and masking

Included participants were 1:1 randomly assigned to the treatment or control group according to a computer-generated randomization list. Assessors were blinded to the participants' allocation.

Procedures

After receiving detailed information regarding study procedure and signing an informed consent form, participants underwent a baseline evaluation which included a review of their medical history, a physical examination, a psychological interview by two senior clinicians, questionnaires and brain imaging. HBOT was given in addition to the patients' pre-inclusion psychotherapy. Participants in the control group continued with their pre-inclusion psychotherapy program and did not receive any hyperbaric treatment. No additional psychotherapy or trauma focused therapy was given as part of the study protocol.

Participants were evaluated at baseline and after three months of HBOT or control.

HBOT: Participants were treated in a multiplace chamber (HAUX-Life-Support GmbH) for a total of 60 daily sessions, five days a week. Each session consisted of 90 minutes exposure to 100% oxygen at 2 ATA with five-minute air breaks every 20 minutes.

Participants in both treatment and control groups continued their psychological and pharmacological treatments as they did before their inclusion. Any changes in the frequency of psychological treatments or pharmacotherapy doses were reported and documented. Monthly meetings with study investigators were scheduled during both treatment and control periods. Unscheduled visits were provided as needed.

Outcomes

The primary objective was defined as the change in the clinician-administered DSM-V (CAPS-V) PTSD scale score from baseline. The brief symptom inventory–18 (BSI-18), and Beck depression inventory-II (BDI-II) questionnaires served as secondary clinical endpoints. Changes in brain MRI diffuse tensor imagine (DTI) sequence and n-back task in functional MRI (fMRI) were also analyzed as secondary endpoints.

CAPS-V is a structured interview-based test that consists of 30 items. Items are rated on a 0 to 4 severity scale. Twenty of the items reflect the severity of DSM-V PTSD symptoms and served as the primary endpoint. The score ranges between 0 and 80, with higher scores indicating more severe PTSD symptoms. The interview was administered by a study investigator, under the supervision of the study psychiatrist at baseline and 1 to 4 weeks after the end of the HBOT or control period.

In addition, participants completed the following questionnaires at baseline and 1 to 4 weeks after the end of the study period:

Beck depression inventory II (BDI-II)—BDI-II is a widely used psychometric tests for measuring the severity of depression. It consists of 21 multiple-choice questions and a self-report inventory about how the subject has been feeling in the last week. Each answer is scored on a scale value of 0 to 3. The scored ranges between 0 and 63, with higher scores indicating more severe depression symptoms.

The brief symptom inventory–18 (BSI-18)—The BSI-18 contains 18 items in three symptom scales: somatization (6 items), depression (6 items), and anxiety (6 items). Each item is rated on the same 0 to 4 scale that reflects symptom severity in the last seven days, and the sum of all responses yields a global severity index (GSI). Scores range between 0 and 72, with the higher scores indicating worse symptoms.

Imaging data acquisition. MRI scans were performed on a MAGNETOM Skyra 3T Scanner, configured with a 20-channel receiver head coil (Siemens Healthcare, Erlangen, Germany). Functional imaging data consisted of 128 volume measurements of gradient-echo (EPI) blood oxygen level dependent (BOLD) contrast sequences. Scan parameters: TR = 3000 ms, TE = 30 ms, flip angle = 90˚, voxel size = 3.0 x 3.0 x 3.0 mm, distant factor = 25%, FOV = 192 mm^2, within slice resolutions of 64×64, and 36 contiguous slices parallel to the AP-PC plane. Diffusion whole brain images were acquired with the following parameters: 63 axial slices, slice thickness = 2.2 mm, voxel size = 1.8 x 1.8 mm, TR = 10,300 ms, TE = 89 ms, and matrix = 128 x 128 mm. Diffusion gradients were applied along 30 noncollinear directions (b = 1000 s/mm^2) and one volume without diffusion weighting. T1-weighted images were acquired with 3D MPRAGE sequences in sagittal orientation with 0.9 mm isotropic resolution. Sequence parameters: TR = 2,000 ms, TE = 2.41 ms, flip angle = 8˚, TI = 928 ms, FOV = 245 x 245, and 192 contiguous slices.

Functional task design. The N-back working memory task is one of the most popular paradigms for functional neuroimaging studies, which refers to temporary storage and manipulation of information. In this study, we used a block design paradigm, consisting of two-condition alternating blocks (0-Back and 2-Back) over a course of eight cycles. Each block consisted of a series of 12 letters. Each letter was presented for 1500 ms, followed by a 1500 ms fixation interval. During the 0-Back condition, participants were asked to respond by pressing a button (ResponseGrip, NordicNeuroLab Inc., Norway) when a target Hebrew letter "ג" was presented. In the 2-Back condition, participants were asked to respond when the current letter was identical to the one presented two trials back. The ratio of target to non-target letters presented in each block is 3/4:12. Participants rehearsed a practice version of the test with a technician outside the scanner to ensure comprehension of the task demands. NordicAktiva,

(NordicNeuroLab Inc., Norway, www.nordicneurolab.no) was used for stimuli presentation, performance accuracy, and response time acquisition.

MRI data analysis. Preprocessing of the raw diffusion data, and calculation of DTI-FA (fractional anisotropy) maps were performed using ExploreDTI, and included corrections for eddy current distortion and participant motion. Spatial normalization was performed for each patient based on the mean diffusion image using the ICBM template, based on T1 contrast. The normalization parameters were applied to the DTI maps. Finally, spatial smoothing with a kernel size of 6 mm full width half maximum (FWHM) was applied. To avoid partial volume bias in the statistical map, and to limit statistical testing to white matter, FA maps were thresholded at 0.2.

Analysis of the time series BOLD data was performed using statistical parametric mapping software SPM12 (Welcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK), through a standard preprocessing procedure. All images were initially slice-time corrected, realigned and resliced using a 6-parameter rigid body spatial transformation to correct head motion, and normalized to the MNI space (Montreal Neurological Institute) by using the unified segmentation normalization algorithm. Finally, spatial smoothing was performed using a 6 mm FWHM Gaussian kernel. The general linear model were applied on a subject level. The design matrix incorporated the task and the six spatial axes movement repressors. The task repressors were modeled as a boxcar function, and were convolved with a canonical hemodynamic response function. A high-pass filter (cutoff of 128 s) was applied to account for slow signal drift. All parametric maps thresholds were set at $P < 0.05$ false discovery rate (FDR) corrected for multiple comparisons. The mean percent BOLD signal change was calculated within spherical regions of interest (6 mm radius of gray matter volume), obtained from this analysis, and centered at the peak t value coordinates.

Statistical analysis

Sample size. Since there was no previous data from prospective studies on the potential beneficial effects of HBOT on PTSD, we followed the recommendations of Hertzog [22] for a sample size determination. A small to medium effect size of 0.3 in a repeated measures ANOVA design, with a power of 85% and an alpha of 5%, a total of 28 participants would be required. Adding a 15% dropout rate would require 32 patients in total.

Data analysis. Unless otherwise stated, continuous data were expressed as means ± standard-deviations. Independent and dependent t-tests with a two-tail distribution were performed to compare variables between and within the two groups, when a normality assumption held according to the Kolmogorov-Smirnov test. Net effect sizes were evaluated using Cohen's d method, defined as the improvement from baseline after HBOT minus control three months improvement divided by the pooled standard deviation (SD) of the composite score. Positive effect sizes indicate improvement. Categorical data were expressed in numbers and percentages and compared by chi-square/Fisher's exact test to identify significant variables. A value of $P < 0.05$ was considered significant. Continuous parameters correlations were performed using the Pearson correlation analysis.

To evaluate HBOT's effect, a mixed-model repeated-measure ANOVA model was used to compare post-treatment and pre-treatment data. The model included time, group and the group-by-time interaction. Non-imaging data analysis was followed by the Bonferroni post-hoc correction.

Brain imaging maps were analyzed using a voxel-based method to generate statistical parametric maps. Group parametric maps were corrected using the Benjamini–Hochberg False Discovery Rate (FDR) method [23]. A mixed design repeated measure ANOVA model was used to test the main interaction effect between time and group implemented in SPM

software (version 12, UCL, London, UK). A sequential Hochberg correction [24] was used to correct for multiple comparisons ($P < 0.05$).

Data was analyzed using SPSS software (version 22.0), and the Matlab R2019b (Mathworks, Natick, MA) Statistics Toolbox.

Results

Between March 2018 and April 2019, 50 subjects were recruited, and 15 who did not fit the study criteria were excluded. Accordingly, 35 subjects were randomized to the HBOT (N = 18) or control (N = 17) groups. As detailed in Fig 1, one patient allocated to HBOT was not able to cooperate with the treatment protocol and preferred to stop the treatment after 20 sessions, and three patients had frequent treatment stoppages because of upper respiratory tract infections (could not equilibrate the ear pressure). Two patients from the control group refused to attend the scheduled meetings and the final analysis. Therefore, of the 35 test subjects, 14 completed the HBOT protocol and 15 completed the control protocol.

Baseline patient characteristics are summarized in Table 1. The mean age at baseline was 39.3 ± 8.1 and 32.4 ± 9.2 and the mean time from last combat exposure was 11.5 ± 5.8 and 10.3 ± 6.7 years for the HBOT and control groups, respectively. The baseline global cognitive score was on the normal range expected for the patients' age and gender, 99.4±6.2 and 98.5 ±8.7 in the HBOT and control group respectively, p = 0.75.

Primary endpoint

Analysis of the CAPS score are summarized in Table 2. At baseline, there were no differences between the groups in any of the CAPS score parameters. A significant improvement in total CAPS score by 17.7 points (CI 11.3–24.1), with group by time interaction (F = 30.57, $p<0.0001$, Net effect size = 1.643, Supporting information), was demonstrated in the HBOT group. Additionally, the HBOT group had significant improvements in all of the subcategories of the CAPS score (Table 2) (Fig 2). No differences in total CAPS scores or in any of the subcategories were seen in the control group.

Secondary endpoints

Questionnaire results are summarized in Table 3. At baseline, there were no significant differences in all questionnaire domains. Significant group-by-time interactions (F = 5.72,

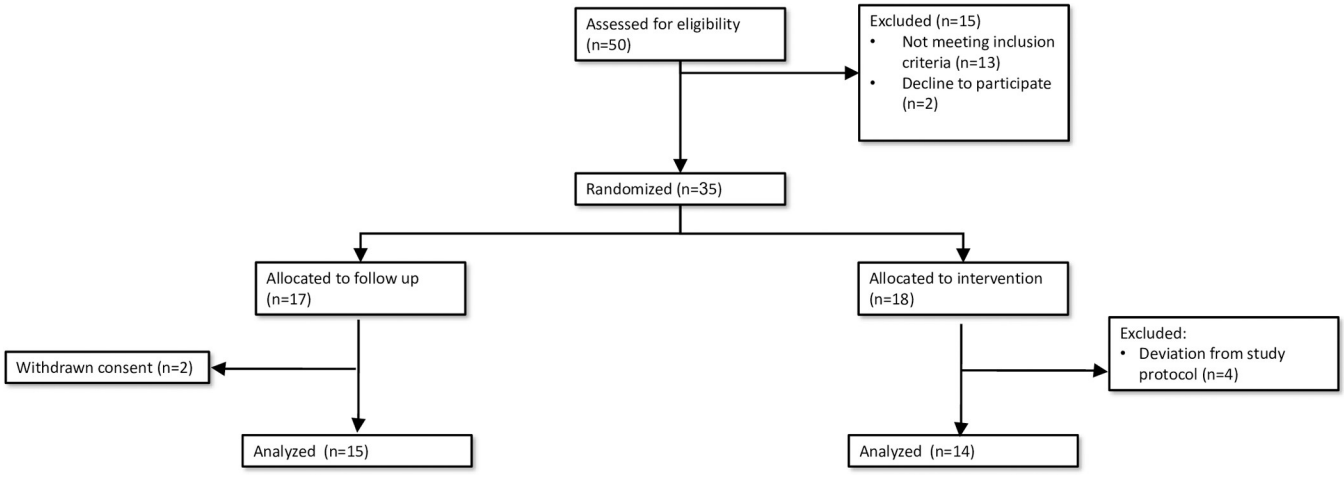

Fig 1. Study flowchart.

https://doi.org/10.1371/journal.pone.0264161.g001

Table 1. Patient characteristics.

	Treatment Group	Control Group	*P*-value
N	14	15	
Age (y)	39.3±8.1	32.4±9.2	0.084
Military exposure (y)	6.8±3.6	5.2±4.8	0.33
Time from last combat exposure (y)	11.5±6.1	11.1±6.4	0.85
Total CAPS score	46.6±11.5	49.5±10.7	0.50
Mild PTSD (20–39)	3(21%)	2(13%)	0.65
Moderate PTSD (40–59)	10(71%)	11(73%)	1.00
Severe PTSD (60–79)	1(7%)	2(13%)	0.97
Education (y)	14.2±2.2	13.7±2.5	0.58
Life partner	9(64%)	6(40%)	0.27
Working	6(43%)	8(53%)	0.71
Global cognitive score*	99.4±6.2	98.5±8.7	0.75
Current major depression*	10(71%)	13(86%)	0.39
History pharmacotherapy	13(93%)	12(80%)	0.59
History of psychotherapy			
PE	5(36%)	4(27%)	0.69
EMDR	10(71%)	9(60%)	0.69
CBT	14(100%)	13(87%)	0.48
Current medications			
SSRI/SNRI	8(57%)	8(53%)	1.00
BDZ	6(43%)	6(40%)	1.00
Anti-psychotic	4(29%)	4(27%)	1.00
Cannabis	12(86%)	10(67%)	0.39
Cannabis (g/ month)	31.4±19.1	25.0±20.8	0.39

* normalized scores presented on an IQ-style scale, where 100 is the mean normalized score and one standard deviation of 15 points.

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Table 2. CAPS measures results.

	HBOT ARM (N = 14)				CONTROL ARM (N = 15)								
	Baseline	**Post HBOT**	**Change [95% CI]**	**3 Months P value**	**Baseline**	**Control**	**Change [95% CI]**	**3 Months P value**	**Baseline**	**Change**	**Cohen's d***	**ANOVA (Group-by-Time) Interaction**	
												F	**P**
B. Intrusion symptoms	12.2±3.8	6.6±4.7	-5.6 [-7.7, -3.6]	**0.000**	12.9±2.6	13.1 ±2.1	0.3 [-1, 1.5]	0.658	0.610	**0.000**	1.741	28.9	**0.000**
C. Avoidance symptoms	4.5±1.7	2.3±1.8	-2.2 [2.9, -1.5]	**0.000**	4.5±1.8	5.0±1.4	0.5 [-0.5, 1.4]	0.313	0.960	**0.000**	1.797	23.4	**0.000**
D. Cognitions and mood symptoms	17.5±3.7	11.1±7.4	-6.4 [-10.2, -2.6]	**0.003**	16.8±5.6	17.5 ±3.8	0.7 [-1.2, 2.6]	0.465	0.700	**0.001**	1.109	13.3	**0.001**
E. Arousal and reactivity symptoms	12.3±4.5	9.0±5.6	-3.4 [-6.1, -0.6]	0.022	15.3±3.2	15.9 ±3.6	0.7 [-0.6, 1.9]	0.265	0.060	**0.008**	0.865	8.5	**0.007**
T. Total	46.6 ±11.5	28.5 ±17.4	-18.1 [-25.4, -10.8]	**0.000**	49.5 ±10.7	51.5 ±8.4	2.0 [-1.3, 5.3]	0.211	0.500	**0.000**	1.643	30.6	**0.000**

Data are presented as mean ± SD; CI, confidence interval; Bold, significant after Bonferroni correction; * Cohen's d net effect size.

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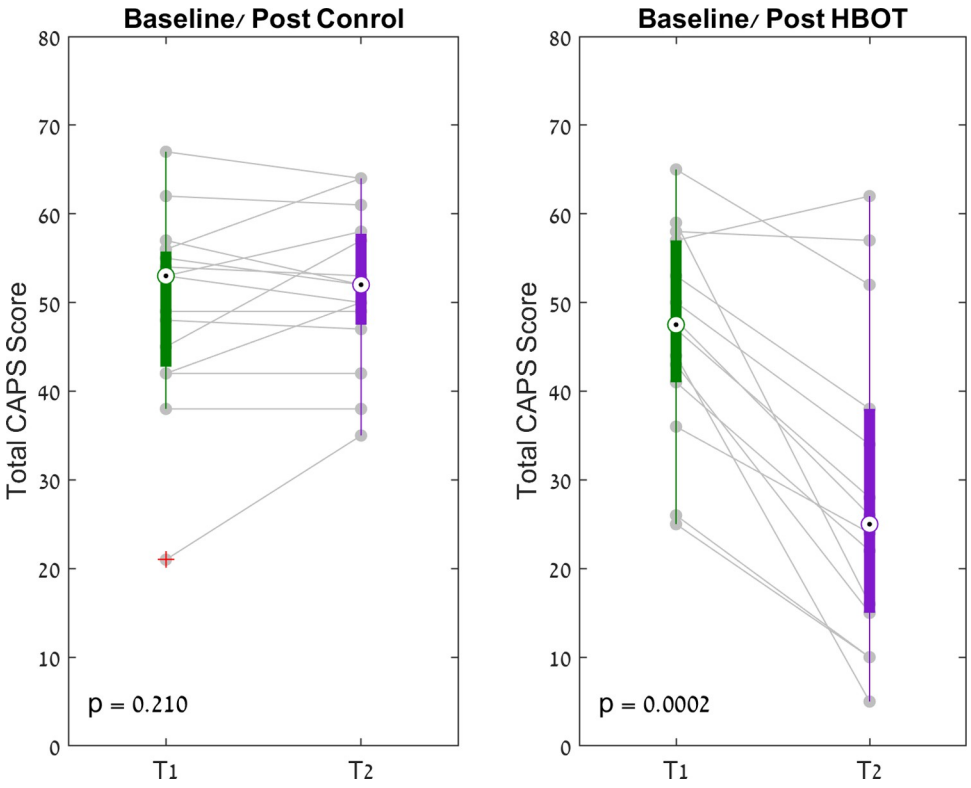

Fig 2. CAPS scores paired box plot. The central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. + Symbols indicate outliers.

https://doi.org/10.1371/journal.pone.0264161.g002

Table 3. Questionnaire results.

	HBOT ARM (N = 14)				CONTROL ARM (N = 15)								
	Baseline	Post HBOT	Change [95% CI]	3 Months P value	Baseline	Control	Change [95% CI]	3 Months P value	Baseline	Change	Cohen's d*	ANOVA (Group-by-Time) Interaction	
												F	P
BSI													
Total	38.0 ± 13.0	27.0 ± 16.0	-11.0 [-19.2, -2.8]	**0.012**	44.3 ± 7.9	43.8 ± 10.9	-0.5 [-5.5, 4.6]	0.846	0.134	0.024	0.890	5.7	0.020
Somatization	10.0 ± 5.5	7.6 ± 5.4	-2.3 [-5.2, 0.4]	0.092	12.8 ± 3.4	12.4 ± 5.0	-0.4 [-2.9, 2.1]	0.739	0.120	0.272	0.420	1.3	0.270
Anxiety	14.3 ± 5.1	10.2 ± 6.4	-4.1 [-7.6, -0.5]	0.027	17.5 ± 3.4	16.9 ± 3.6	-0.6 [-2.8, 1.6]	0.565	0.062	0.079	0.680	3.3	0.080
Depression	13.7 ± 4.8	9.1 ± 5.5	-4.6 [-7.3, -1.8]	**0.003**	14.0 ± 3.0	14.5 ± 3.8	0.5 [-1.4, 2.5]	0.571	0.854	**0.003**	1.220	10.7	**0.003**
BECK	24.4 ± 6.8	18.1 ± 9.5	-6.3 [-9.7, -2.9]	**0.002**	26.8 ± 6.7	27.5 ± 7.7	0.6 [-3.5, 4.7]	0.757	0.357	**0.010**	1.030	7.7	**0.010**

Data are presented as mean ± SD; CI, confidence interval; Bold, significant after Bonferroni correction; * Cohen's d net effect size.

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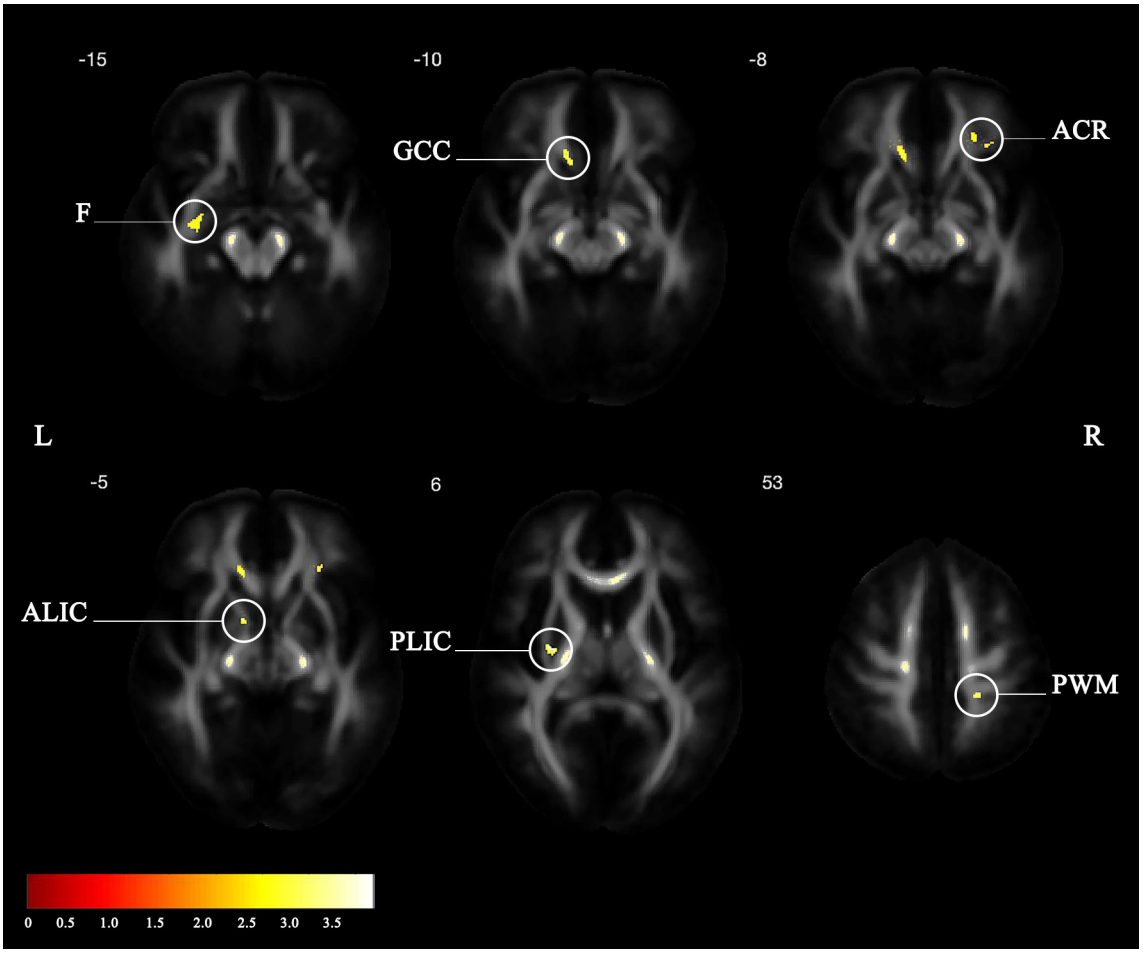

Fig 3. Statistical parametric maps of the group-by-time interaction for the white matter FA. (F: Fornix; GCC: Genu of corpus callosum; ACR: Anterior corona radiata; ALIC: Anterior limb of internal capsule; PLIC: Posterior limb of internal capsule; PWM: Parietal white matter).

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$P = 0.024$, Net effect size = 0.89) were demonstrated in total BSI-II scores and in the depression subcategory (F = 10.72, $P = 0.003$, Net effect size = 1.22, S2 Table). A trend towards improvement was demonstrated in the somatization and anxiety subcategories, but the improvements did not reach statistical significance (F = 1.26, $P = 0.27$ and F = 3.34 and $P = 0.079$ for somatization and anxiety respectively). In addition, a significant group-time interaction (F = 7.65, $P = 0.01$, Net effect size = 1.03, Supporting Information) was demonstrated in the total BDI-II score after HBOT. In addition, statistically significant correlations were found between the percent change in total CAPS Score and the percent change in BDI-II and BSI-18 questionnaires (r = 0.62–0.67, $p<0.0004$, Supporting Information).

Regional brain microstructure integrity. One patient did not perform MRI due to retained metal shrapnel in the lungs that was detected in a chest X-ray after inclusion. DTI-MRI was analyzed from 13 patients from the HBOT group and from 15 patients from the control group. Voxel-based DTI analysis of brain white-matter FA maps is shown in Fig 3 and in Table 4. Significant group-time interactions were demonstrated in the HBOT group compared to the control group in frontal white-matter fiber bundles connecting the thalamus and frontal lobe (anterior limb of internal capsule L and corona radiata R) and in the genu of corpus callosum, connecting between the frontal lobes. In the parietal lobe, significant clusters were found in

Table 4. Statistical parametric maps of the group-by-time interaction for the white matter FA (L left, R right, X, sagittal, Y, coronal, Z, axial, coordinates refers to Montreal Neurological Institute.

Peak Region	Cluster Size	x	y	z	t Value	*p* Value
L Posterior limb of internal capsule	79	-29	-8	6	3.67*	0.0001
R Parietal white matter	93	21	-34	53	3.33*	0.001
L Anterior limb of internal capsule	46	-11	5	-5	3.22*	0.001
Genu of corpus callosum	91	33	32	-8	3.07	0.002
R Anterior corona radiate	228	-13	30	-5	3.04	0.002
L Fornix	111	-28	-6	-15	2.8	0.004

* Satisfied Hochberg correction $p<0.05$).

https://doi.org/10.1371/journal.pone.0264161.t004

parietal white-matter (adjacent to the superior longitudinal fasciculus) and in the anterior limb of the internal capsule and cerebral peduncle (ascending and descending motor and sensory fibers). Significant clusters were also found in the fornix, in an area adjacent to the hippocampus.

Only the posterior and anterior limbs of the internal capsule and parietal white-matter passed the correction to multiple comparisons ($p<0.05$, corrected). However, since this was a small sample size and we evaluate the treatment effect including a control group, we included clusters larger than 40 voxels passing $p<0.01$ uncorrected.

Task-related functional imaging results. Brain activity of the PTSD patients was obtained from 13 patients from the HBOT group, and 15 patients from the control group patients. The whole-brain task related activation (2-back > 0-back) at baseline and after HBOT/control sessions is shown in Fig 4 ($P < 0.05$, FDR corrected). The two-sample t-test analysis, performed between groups at baseline, yielded no significant functional differences. Brain clusters with a significant group-by-time interaction effect ($p<0.05$, Hochberg corrected) are listed in Table 5. Improved activity after HBOT was demonstrated in the left dorsolateral prefrontal, middle temporal and temporal gyri as well as in both thalami, left hippocampus and left insula. No significant functional differences between the two control group fMRI sessions were found (Fig 4). Statistically significant correlations were demonstrated between mean percent BOLD signal changes in peak significantly activated regions and percent change in total CAPS score ($r = 0.42–0.67$, $p<0.05$, Supporting Information).

Safety and side effects

HBOT for PTSD was well tolerated with seven documented events of mild and spontaneously resolved middle ear barotrauma. Seven subjects from the HBOT group had an unexpected surfacing of new memories during the HBOT course. In all accept one participant memories surfaced gradually, during the second half of the treatment course (after 25–35 sessions of HBOT) in peaces that gathered to whole clear picture of the event. In one of the participants, the new memory appeared abruptly as flashback, following the fifth HBO session.

The recovery of the memories was usually accompanied by severe distress followed by integration of the memory and resolution of the distress. Patients who reported surfacing of new memories were interviewed and their symptoms and memories were documented.

No intentional questioning regarding memory surfacing was done, and thus memory surfacing could not be ruled out in other patients who might not reported as it.

Discussion

The current study evaluates for the first time in a prospective controlled study, the effect of HBOT on veterans suffering from treatment resistant PTSD. HBOT induced significant

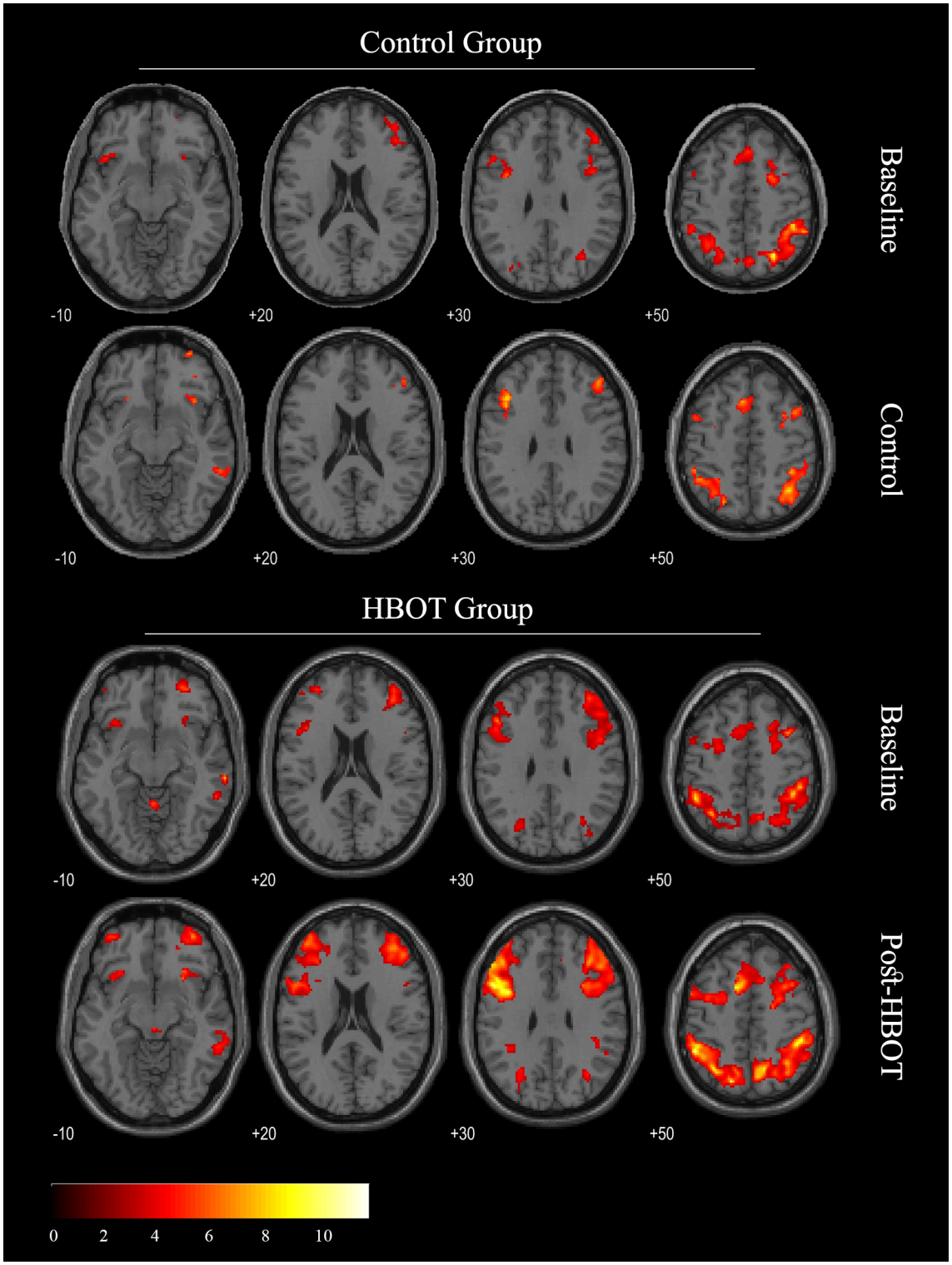

Fig 4. Main regional loci of brain activation in a verbal working memory task (2-Back– 0-Back) Group analysis, $p < 0.05$, FDR corrected.

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Table 5. Local maxima of brain activation (2-Back– 0-Back): Group-by-time interaction.

Peak Region	BA	Cluster Size	x	y	z	t value	*p* value
R Fusiform Gyrus	20	68	44	-26	-24	4.85	0.0000
L Thalamus	50	78	-12	-10	8	4.79	0.0000
R Thalamus	50	64	12	-28	2	4.67	0.0000
L Hippocampus	54	95	-34	-30	-12	4.64	0.0000
L Temporal Gyrus	21	48	-54	-44	10	4.24	0.0001
L Insula	13	21	-44	-2	-8	3.90	0.0001
L Dorsolateral Prefrontal	9	20	-28	40	44	3.89	0.0002
L Medial Posterior Parietal	7	59	-16	-70	40	3.89	0.0002
R PCC	23	30	0	-14	34	3.87	0.0002
L Superior Temporal Gyrus	38	20	-44	4	-18	3.82	0.0002
L Middle Temporal Gyrus	39	21	-30	-76	34	3.70	0.0003

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reductions in the PTSD symptoms and the associated depression as assayed by CAPS-V, BDI and BSI questionnaires. The marked clinical improvement was associated with improved brain functionality and microstructural integrity as evident by fMRI and DTI-MRI.

HBOT's potential beneficial effects on combat associated PTSD was demonstrated in previous studies that evaluated its effect on TBI and included PTSD related symptoms as one of the study endpoints [14–20]. The last study from BIMA study team [20] clearly demonstrated pronounced effects of HBOT on the subgroup of veterans who had concomitant PTSD symptoms, with PTSD effected veterans benefiting more from HBOT than veterans without PTSD. Since TBI and PTSD share common symptoms such as nervousness, sleep disorders, and impaired cognitive function, it is difficult to assign the improvement to either one of the pathologies. In the current study, only patients with PTSD who did not have TBI were included, and any history of TBI served as an exclusion criterion. Thus, both clinical and radiological effects demonstrated in the current study can only be associated to HBOT's effects on PTSD.

PTSD's current treatment success rate is poor. Trauma-focused psychotherapy is currently the treatment of choice while pharmacotherapy is added when psychotherapy is insufficient. However, up to 50% fail to respond to any of the available treatments. The lack of effective treatments might have contributed to the successful recruitment in the current trial, despite the demanding treatment protocol.

Brain imaging changes can serve as markers for poor treatment responses [25]. A review of the published studies using high resolution and functional MRI techniques, indicate failure of the frontal-limbic circuit as PTSD's hallmark [5–8]. Diminished prefrontal inhibition and a hyperactive amygdala in response to both trauma-related [5,6] and non-trauma-related [6] stimuli in PTSD patients are consistent with diminished prefrontal inhibition of fear circuitry. Functional MRI studies using N-back tasks, demonstrate under-recruitment of prefrontal neurons, mostly dorsolateral PFC, and parietal cortex. Changes in brain microstructure, demonstrated by DTI-MRI, including reduced white-matter integrity, typically seen in the left frontal and temporal tracts and thalamo-cortical tracts, are also part of the fronto-limbic circuit failure [26,27]. In addition, impaired inter-hemispheric connectivity, as evident by decreased FA values in the genu of the corpus callosum, was also described among PTSD patients [28].

In the current study, using fMRI and the N-back paradigm, restoration of fronto-limbic integrity was demonstrated, with improved recruitment of the left dorsolateral PFC, of both thalami and of the left hippocampus. Improved microstructural integrity between frontal and parietal or temporal regions was also demonstrated using MRI-DTI as increased FA in the anterior limb of the left internal capsule, right corona radiata and fornix. Restoration of the

fronto-limbic circuit may explain the significant clinical improvement related to emotional regulations as reflected by a decrease in total, and in particular, criterion E of the CAPS score. Since the intrusive symptoms can also be a result of the cortex's failure to inhibit the limbic system [7], restoration of fronto-limbic circuit may also explain the significant clinical improvements in criterion B of the CAPS score.

In addition to the fronto-limbic circuit, HBOT induced significant improvements of hippocampal activity as demonstrated by fMRI and the integrity of its connections, assessed as improved FA in the fornix in DTI imaging. The hippocampus has a central role in PTSD pathogenesis, and it may serve as an important treatment target. The hippocampus is involved in memory performance and in information processing deficits observed in PTSD patients [29]. Hippocampal integrity is also crucial for fear extinction [30].

Studies on hippocampal cell culture show that HBOT can directly induce orthodromic activity and neural plasticity [31]). In addition, the dentate gyrus of the hippocampus serves as one of the major niches for endogenous neuronal stem cells (NSC), and recent reports demonstrated HBOT's effect on mitochondrial signaling and regulation of NSC proliferation and differentiation [32].

One of the interesting findings in the current study, was the surfacing of inaccessible memories in half of the patients from the HBOT group. A similar HBOT effect on childhood sexual abuse related repressed memories was previously reported in a fibromyalgia patient study [13]. It is known that direct triggering of the hippocampus by deep brain stimulation can induce surfacing of inaccessible memories [33]. Therefore, the surfacing of memories in our veteran population can be related to the direct neuroplasticity effect detailed above at the hippocampal level.

Study limitations

First, a cohort of 35 randomized patients is rather small. Even though the results are significant, larger scale clinical trials are required to confirm the finding presented. Second, even with randomization and blinded imaging analysis, participants were not blinded to the treatment arm, due to the inherent difficulty of conducting a sham control in HBOT trials [9,2] This could possibly affect the questionnaires. However, the chronic unremitting nature of PTSD among our participants together with the correspondence between the clinical improvement and brain functional and structural improvements as evident by the brain imaging, substantiates the clinical findings. In addition, the unexpected recovery of memories and accompanied distress during the second half of the treatment course, strongly point to HBOT's direct biological effects on this cohort of PTSD patients.

To conclude. This prospective randomized controlled trial demonstrates that HBOT can induce neuroplasticity and improve PTSD related symptoms of veterans suffering for treatment resistant PTSD. HBOT improved both the brain function and brain microstructure in regions typically involved in PTSD pathogenesis. The correlation between the clinical improvement and the changes in the brain functionality and microstructure can shed additional important light on the biology responsible for treatment resistant PTSD.

Supporting information

S1 Checklist. CONSORT 2010 checklist of information to include when reporting a randomised trial*.
(DOC)

S1 Fig. Scatter plot of the correlations between percent change in total CAPS Score and the percent change in BDI and BSI questionnaires scores. r is Pearson's correlation coefficient, $p < 0.0004$ for all comparisons.
(TIF)

S2 Fig. Scatter plot of the relative percent BOLD signal change in peak significantly activated regions, and the percent change in total CAPS score. r is Pearson's correlation coefficient, $p < 0.05$ for all comparisons.
(TIF)

S3 Fig. Questionnaire scores paired box plot. The central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. + Symbols indicate outliers.
(TIF)

S1 Table. Total CAPS score repeated measures ANOVA.
(DOCX)

S2 Table. Questionnaire repeated measures ANOVA.
(DOCX)

S1 Dataset.
(XLSX)

S1 File.
(PDF)

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Israeli Breakthrough in Treating PTSD.pdf
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Position: FAV

Israeli Breakthrough in Treating PTSD

World first: TAU-led team shows success of oxygen therapy in alleviating symptoms of PTSD in military veterans

22 February 2022

Researchers from Tel Aviv University and Israel's Shamir Medical Center were able to successfully relieve the symptoms of post traumatic stress disorder (PTSD) in military combat veterans using a new protocols of hyperbaric oxygen therapy (HBOT). In a controlled clinical trial involving Israeli army veterans who suffered from treatment-resistant PTSD, the approach demonstrated significant improvement in all classes of symptoms.

According to the World Health Organization (WHO), almost 4% of the global population, and 30% of all combat soldiers, develop PTSD.

Hyperbaric medicine involves treatments in a pressurized chamber where atmospheric pressure is higher than sea-level pressure and the air is rich with oxygen. Considered a safe form of treatment, hyperbaric oxygen therapy is already used for a range of medical conditions. Evidence gathered in

recent years indicates that special hyperbaric protocols can improve the supply of oxygen to the brain, thereby enhancing the generation of new blood vessels and neurons. It must be noted that HBOT treatments require the evaluation and supervision of qualified physicians. Moreover, for medical indications it should be given using a certified chamber with appropriate quality assurance using the exact studied treatment protocols.

The breakthrough research was led by Prof. Shai Efrati, Dr. Keren Doenyas-Barak, and Dr. Amir Hadanny of Tel Aviv University's Sackler Faculty of Medicine and Sagol School of Neuroscience in cooperation with Shamir Medical Center. The team also included Dr. Ilan Kutz, Dr. Merav Catalogna, Dr. Efrat Sasson, Gabriela Levi and Yarden Shechter of Shamir Medical Center.

Unloading Pain for a Better Future

The study included 35 combat veterans of the Israel Defense Forces (IDF) who suffered from PTSD that was resistant to both psychiatric medications and psychotherapy.

"The veterans were divided into two groups: one group received hyperbaric oxygen therapy while the other served as a control group," explains Dr. Keren Doenyas-Barak of Shamir Medical Center. "Following a protocol of 60 treatments improvement was demonstrated in all PTSD symptoms, including hyper-arousal, avoidance, and depression. Moreover, both functional and structural improvement was observed in the non-healing brain wounds that characterize PTSD. We believe that in most patients, improvements will be preserved for years after the completion of the treatment."

"This study gives real hope to PTSD sufferers. For the first time in years the study's participants, most of whom had suffered from severe PTSD, were able to leave the horrors behind and look forward to a better future."

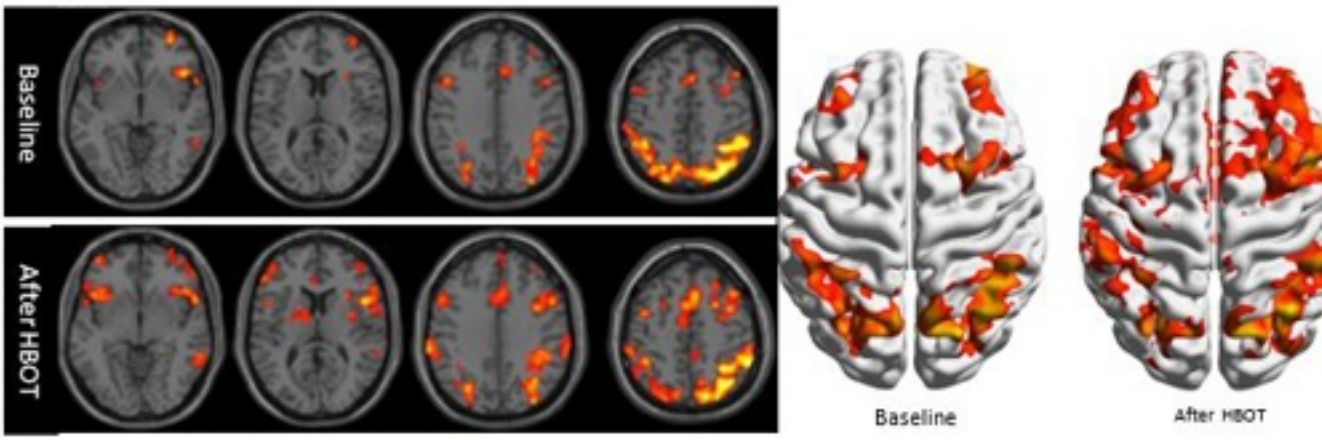

Illustration: Clinical example of functional brain imaging by fMRI. The reduced brain activity in the frontal lobes of the brain (responsible among others for emotional regulation and executive functions) and in hippocampus (responsible for memories functions) is improved after Hyperbaric Oxygen Therapy (HBOT).

Emotional Trauma Can Cause Physical Damage

"Today we understand that treatment-resistant PTSD is caused by a biological wound in brain tissues, which obstructs attempts at psychological and psychiatric treatments," explains TAU Prof. Shai Efrati. "With the new hyperbaric oxygen therapy protocols, we can activate mechanisms that repair the wounded brain tissue. The treatment induces reactivation and proliferation of stem cells, as well as generation of new blood vessels and increased brain activity, ultimately restoring the functionality of the wounded tissues. Our study paves the way to a better understanding of the connection between mind and body."

"Our results indicate that exposure to severe emotional trauma can cause organic damage to the brain," says Prof. Efrati. "We also demonstrate for the first time that direct biological treatment of brain tissues can serve as a tool for helping PTSD patients. Moreover, our findings may be most significant for diagnosis. To date, no effective diagnostic method has been developed and diagnosis of PTSD is still based on personal reports which are necessarily subjective – leading to many clashes between the suffering veterans and the authorities responsible for treating them. Think of a person who comes to the emergency room with chest pains. The pain might be caused by either a panic attack or a heart attack, and without objective EKG and blood tests, the doctors might miss a heart attack. At present we are conducting continuing research in order to identify the biological

fingerprint of PTSD, which can ultimately enable the development of innovative objective diagnostic tools."

Prof. Shai Efrati

Prof. Efrati is an Associate Professor at TAU and director of the Sagol Center for Hyperbaric Medicine and Research at Shamir Medical Center. He is also the co-founder and Chair of the Medical Advisory Board at Aviv Scientific LTD, a company that applies the hyperbaric oxygen therapy protocols developed from his team's research to enhance the brain and body performance of aging adults.

Maryland TBI Veteran Economic Cost Impact 1-19-22.
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Position: FAV

The Brain-Wounded Veteran
Brain Drain in Maryland

CARE FOR HIM WHO SHALL HAVE BORNE THE BATTLE

~ Abraham Lincoln

Prepared for Senator Sarah K. Elfreth, and the State of Maryland Legislature

By

The TreatNOW Coalition, Eric Koleda (National Director – Legislative Efforts)
www.treatnow.org

January 2022

Executive Summary

The costs of the twenty-year wars in Afghanistan, Iraq, Syria, and Pakistan are staggering. According to a recent study, they have cost American taxpayers $6.4 trillion.[1] In addition, the Watson Institute of International and Public Affairs report at Brown University finds that more than 801,000 people have died directly from fighting.[2] As of February 2, 2021, over 7,053 US personnel have been killed in Iraq and Afghanistan. Moreover, traumatic Brain Injuries, the "invisible wounds," and the "signature injuries" to US service members are over eight hundred thousand, in addition to the tens of thousands of visibly wounded combatants.

Realistic estimates of TBI-related costs in the military are achieved through comprehensive long-term studies that have never been produced to our knowledge. Actual cost data at the level of individual patients is required. Variables included specific TBI characteristics, treatments, comorbidities, health consequences, rehabilitation needs, and long-term disability. Such a study must follow injured Veterans over a long period to collect accurate cost data for all services they receive. An investigation must also account for the effects of improvements in technology and treatment on costs to ensure compatibility of cost estimates from different periods. Information about the economic consequences of TBI-related mortality must be obtained from families of those Veterans who died from TBIs. Costs in this document were conservatively understated scaled as not to overstate the economic impact

Over 98 percent of the current pharmacologic treatment for TBI and PTSD are NOT FDA approved and off label. Yet, treating TBI with off-label drugs, processes, devices, and protocols not authorized by the FDA for TBI is a continuing formula for failure to prevent, much less reverse, the TBI Veteran suicide and opioid epidemic. In addition, failures of a growing number of psychological interventions have also proved ineffective in reversing the suicide epidemic. As a result, costs and suicides continue to escalate. In fact, by VA accounting, the national suicide rate has steadily increased since 2005.

The current estimated annual societal economic impact by Maryland TBI veterans is $584,586,024 (Table 1) *that* live with an untreated, undiagnosed, or misdiagnosed TBI. This calculated loss of economic activity is spread across a complex of known impacts. It includes Veteran caregiver cost, drug, and opioid-induced costs, including loss of state and federal income tax, loss of state and federal tax revenues from TBI suicides, pharmaceutical costs,

[1] https://abcnews.go.com/International/wireStory/counting-costs-americas-20-year-war-afghanistan-77414628
[2] Watson Institute International & Public Affairs, Brown University Cost of War, Human Cost of Post 9/11 Wars: Lethality and Need for Transparency, November 2018, Neta C Crawford

unemployment, homelessness, incarcerations, loss of state sales taxes, state vehicle taxes, non-taxable VA and Social Security disability payments, incarceration state costs, and pharmaceutical costs. Therefore, a conservative approach to the total economic impact for each of the cost elements described herein is used in the following data.

Treating and healing brain wounds, now possible, can tip the scales to reverse the suicide epidemic among service members and break accelerating costs. The financial benefits to the VA and US Federal, State, County budgets are significant. The VA Mission Act of 2018, Public Law 116-171, S.785, the Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019, The Executive Order on a National Roadmap to Empower Veterans and End Suicide support and provide for TBI Veterans accessing this treatment.

2021 Estimated Maryland TBI Veteran Economic Societal Cost Impact

Revenue Stream	Estimated Type Revenue	Total Estimated Cost
Total Veteran Caregiver Cost (CG)	TBI CG Cost Per Yr 21,780 x $13,581	$295,794,180.00
TBI Veteran Opioid Use Disorder	State Income Tax Revenue Loss	$6,251,659.00
TBI Veteran Opioid Use Disorder	Federal Income Tax Revenue Loss	$26,770,406.00
TBI Veteran Opioid Use Disorder	VA Disability Payments(non-taxable)	$17,967,969.00
TBI Veteran Opioid Use Disorder	Social Security Disability (non-taxable)	$19,382,400.00
TBI Veteran Pharmaceutical Cost	TBI Veteran Pharma Cost Per Yr Per Vet	$8,621,111.00
TBI Veteran Suicide	State Incoome Tax Revenue Loss	$678,114.00
TBI Veteran Suicide	Federal Income Tax Revenue Loss	$2,903,773.00
TBI Veteran Suicide	Social Security Disability (non-taxable)	$2,102,400.00
TBI Veteran Suicide	VA Disability Payments(non-taxable)	$1,948,977.00
TBI Unemployed Veterans	Unemployed State Income Tax Loss	$17,078,267.00
TBI Unemployed Veterans	Unemployed Federal Income Tax Loss	$73,131,338.00
TBI Homeless Veterans	State Incoome Tax Revenue Loss	$3,418,440.00
TBI Homeless Veterans	Federal Income Tax Revenue Loss	$14,638,200.00
TBI Veteran Incarcerations	State Veteran Incarceration Cost	$51,295,968.00
TBI Veteran State and Local Taxes	State and Local Property Tax Loss	$13,228,965.00
TBI Veteran State Property Tax	State Vehicle Property Tax Loss	$0.00
TBI Veteran State and Local Sales Tax	State and Local Sales Tax Loss	$29,373,857.00
Maryland Total Estimated Annual Cost Impact		**$584,586,024.00**

Table 1
Note: The cost analysis details for each of the above category sections appear in this report.

TBI Veteran Caregiver Economic Yearly Cost

"The RAND Report reflects 41,163 households contacted, 28,164 (68 percent) of caregivers responded to complete the screener for the survey. Of this group, 1,129 military caregivers and 1,828 civilian caregivers participated, making this study the largest and only nationally represented survey of military caregivers to this date in 2013. The report goes on to indicate there are 5.5 million caregivers in the US, approximately 20 percent or 1.1 million who are caring for persons who served post 9/11."[3] We used a conservative 1.1 million military caregivers as the basis for our analysis. We then used the Maryland percentage of Veterans to the total US Veteran population of 1.98 percent. We applied that same percentage to the US caregivers to estimate the total number of Veteran Caregivers in Maryland. That equates to an estimated 21,780 Maryland caregivers (1,100,000 x 1.98%).

[3] 2014 RAND Report, "Hidden Heroes, America's Military Caregivers

Key findings include that 33 percent of all post-9/11 military caregivers are spouses of the care recipient, 25 percent are the care recipients' parents, for a total of 58 percent being either spouses or parents. In addition, the report identified 64 percent of post-9/11 military care recipients have a mental health or substance use disorder, nearly 50 percent of all post 9/11 military care recipients have depression. Finally, approximately 76 percent of post-9/11 military caregivers are in the labor force but, on average, miss one day of work per week or 52 days per calendar year.

"RAND estimated and assigned an economic value to an hour of family caregiving of $11.16 per hour, 18 hours per week on average, multiplied by 52 weeks in 2013 cost".[4] Using the US average 114 year average inflation rate of 3.24 percent, it equates to $14.51 per hour in 2021, times 18 hours average per week and 52 weeks per year, or on average, $13,581 per year, per caregiver. Using the estimated 21,780 Maryland military caregivers' times the $13,581 estimated annual cost impact per caregiver equates to an estimated **$295,794,180 million per year of unpaid Maryland labor for family TBI Veteran caregivers.**

TBI Veteran Suicide Epidemic (VSE) and Cost

In the last four years, the official government estimate on the number of veterans who die by suicide has gone from 22 a day to 17 a day, according to the latest Veterans Affairs report. But the rate of suicides among Veterans didn't decrease over that span. Instead, how the VA calculated the figures by sorting and presenting did! Instead, outside experts note that the problem has worsened by many standards, particularly during COVID when suicides are up for all categories. The total number of suicides among Veterans has increased four of the last five years on record. From 2007 to 2017, the rate of suicide among Veterans jumped almost 50 percent. Veterans are 1.5 times more likely to die by suicide than Americans who never served in the military. For female Veterans, the risk factor is 2.2 times more likely. ***"Our takeaway from all this is that what we are doing is not working," "Everyone has been focused on this, but we're not seeing results,"*** said Chanin Nuntavong, National Director of Veterans Affairs and Rehabilitation for the American Legion.

A significant study was published in 2016 that throws new light on the difficulty of differentiating between brain injuries caused by either PTSD or TBI. In what is being called a breakthrough study, Dr. Daniel P. Perl and his team at the Uniformed Services University of the Health Sciences in Bethesda, MO, USA [the medical school run by the Department of Defense], have found evidence of tissue damage caused by blasts alone, not by concussions or other injuries. The New York Times calls it the medical explanation for shell shock: preliminary proof of what medicine has been saying without proof for nearly 100 years -- blasts cause physical damage, and this physical damage leads to psychological problems, *i.e.*, PTSD.

Over one billion dollars was spent on research, treatments, and interventions that may or may not have contributed to the small number of infections and deaths. Yet the suicide epidemic and hundreds of thousands of veterans and active duty suffering from brain injuries, coupled with a

[4] The RAND Report, "Hidden Heroes, America's Military Caregivers" dated 2014, page 155-156, Potential Benefits and Costs to Society

suicide rate of 20 per day, for a total estimated at over 48,000 (nearly five combat divisions), has caused no sense of urgency and immediate use of therapies.

Evidence that the VA aims at symptom identification and resolution on a symptom-by-symptom basis – as opposed to holistic, integrated, patient-centered, precision medicine- can be found in the latest update to VA and DoD Clinical Practice Guideline the Management of Concussion-Mild Traumatic Brain Injury. In addition, evolving treatment protocols turn toward isolating individual symptoms and treating those symptoms of brain injury instead of focusing on the cause – the underlying brain injury.

There should be a call for action and change in a significant way. For example, a study of 273,591 veterans (16% with TBI history or 43,775) receiving care from the Department of Veterans Affairs reported a connection between TBI, PTSD, and suicide attempts. The authors found an increase in suicide attempts among those with deployment related TBI than those without TBI (hazard ratio 3.76, 95% CI 3.15 to 4.49).[5] Further analysis showed that psychiatric conditions mediated 83% of the association between TBI and attempted suicide, with PTSD having the most significant impact hazard. So, the November 2018 Defense and Veterans Brain Injury Center Research concluded population-level investigations have consistently found elevated rates of death by suicide, as well as suicide attempts and suicide ideation in individuals with a positive history of TBI.

A systematic review conducted by Bahraini supported an increased risk of suicide among persons with TBI history compared to those with no TBI history.[6] Some non-military studies have reported that the risk of death by suicide maybe three to four times higher for individuals with TBI than for the general population.[7] A surveillance study of 20 years of data from Canadian health and vital statistics databases found that persons with mTBI were three times more likely to die of suicide than someone in the general population.[8] Swedish researchers conducted a large longitudinal study and found that TBI patients are three times more likely to die by suicide when compared to matched controls from the general population without a history of TBI.[9] And the same rate of increase in suicide death one-year post-TBI was found in a study by Harrison-Felix et al.[10] "The DoD is reimbursing for off-label use of FDA Black Box labeled drugs that have been implicated in the marked suicide rate in our injured veterans. These drugs mask symptoms or act as chemical restraint, leaving untouched the underlying brain injury that is repaired by HBOT 1.5."[11] There currently is "NOT" any of the approximately 100 medications routinely prescribed to TBI Veterans that are FDA approved; they are all "off-label" and experimental. How is it oxygen, an FDA-approved drug and not widely used for TBI when used in the medical capacity?

[5] Jennifer R. Fonda et al., A Methodology for Assessing Deployment Trauma and Its Consequences in OEF/OIF/OND veterans: The TRACTS longitudinal prospective cohort study, 2016
[6] Psycnet.apa.org, Suicidal ideation behaviors after traumatic brain injury: A systematic review. Bahraini, Simpson, Brenner, Hoffberg, & Schneider, 2013
[7] Pubmed.ncbi.nim.nih.gov, Suicidality in people surviving a traumatic brain injury: prevalence, risk factors and implications for clinical management. Simpson & Tate, 2007
[8] Pubmed.ncbi.nim.nih.gov Fralick, Thiruchelvam, Tien, & Redelmeier, 2016
[9] Fazel, Wolf, Pillas, Lichtenstein, & Langstrom, 2014
[10] Pubmed.ncbi.nim.nih.gov, Harrison-Felix et al., 2009
[11] Dr. Paul Harch, Suicides in the U.S. Military Personnel, Veterans of War in Iraq and Afghanistan, and the Core Medical treatment for Mild-Moderate Traumatic Brain Injury & PTSD, June 22, 2010, report to Senate Armed Services Committee.

The VA 2005 to 2017 historical suicide report is a revelation. ***We have lost more than 78,000 veterans to suicide over the past 13 years by the VA accounting (Table 3 Page 11).*** That is, by CDC standards, a national epidemic. Approximately 7,300 Veterans have committed suicide each year over the past ten years (73,000), while the number of Veterans of wars declined by about 15 percent. The VA/DoD may not account for veteran suicides if they are not active duty or enrolled in the DoD/VA, so there is a variance in the VA accounting, with actual suicides reported. As recently as four years ago, VA leaders were referencing the "22 a day" statistic regarding Veteran suicide based on partial state death records data and internal estimates. "Between March and August 31, 2020, 144 active-duty Army soldiers killed themselves up from 88 in 184 days."[12] "When Army reservists and national guardsmen have added the figure, it jumped to 200, compared with 166 for last year's period. The rate of suicide currently among active-duty Army soldiers is 36 per 100,000 defense officials said, up from 25.9 deaths per100,000 last year".[13] The military leaders attribute the increase to Covid 19 induced isolation from families suffering from and dying of Covid 19, which has created additional stress and inability to travel.

www.VA.vetdata.gov reported from 2005 through 2017, 78,875 veterans have committed suicide, a thirteen-year average of 6,067 per year. Males accounted for 75,975 of those deaths or 96% of the total. Although the suicide rate in the US Army has traditionally been below the demographically matched civilian rates, it has climbed steadily since the beginning of the conflicts in Iraq and Afghanistan. During these tours, suicide rates among service members rose from 9.9 to 22.7 per 100,000.[14] The Army (53%) and Marines (18%) account for 71 percent of all TBI's incurred by service members since the Iraq and Afghanistan conflicts.

"The number of veteran suicides has exceeded 6,000 every single year between 2008 and 2017, and in 2017, the suicide rate for veterans was 1.5 times the rate for non-veteran adults."[15] The daily suicide rates continue to climb to over 30.5% over the 2005 rates. We can point towards ineffective treatments, program assessments, or the deluge of "more research," or perhaps the symptom-based non-FDA-approved drug treatment protocol for causes. What is not being addressed is the actual root cause, ***that mTBI is a physical brain wound, and protocols prescribing black box off labeled, non-FDA approved drugs by the VA is impacting the suicide rate****. The rate of suicides has continued to climb each year since 2005 unabated.*

"Since late 2001, US military forces have been engaged in conflicts around the globe, most notably in Iraq and Afghanistan. These conflicts have exacted a substantial toll on Soldiers, Marines, Sailors, and Airmen, which goes beyond the well-publicized casualty figures. It extends to the stress that repetitive deployments can have on the individual service member and their family. This stress can manifest itself in different ways—increased divorce rates, spouse and child abuse, mental distress, substance abuse—but one of the most troubling manifestations is suicides, which are increasing across the Department of Defense (DoD)."[16] Oddly, this is the

[12] Reported by Nancy Youssef from the Wall St. Journal
[13] Reported by Nancy Youssef from the Wall St. Journal
[14] DoD, 2011; ncbi.nim.nih.gov, Logan, Bohnert, Spies, Jannausch 2013
[15] The January 23, 2020, article, "Veteran Suicide Rates Remain High Despite Year of Reform" on the www.foxnews.com website
[16] Ramchand et al., The War Within: Preventing Suicide in the US Military

same period we deployed over 4 million troops, including second through fourth tours for our veterans, to Iraq and Afghanistan to combat terrorism, and the reported mTBIs escalated.

"VHA patients with mental health condition or Substance-Use-Disorder (SUD) diagnoses accessed mental health treatment services have higher rates of suicide than other VHA patients."[17] The main finding reflected, "rates of suicide among users of VHA services have remained relatively stable in recent years."[18] With no change in the suicide rates over fourteen years, how can the report reflect the conditions are stable? The suicide rate for VHA users in 2001 was 39.9; in 2014, it was 39.2. *Fourteen years of NO change or improvement in the VA treatment protocol are reflected in the data tracked but relatively stable.* Year over year, despite the carnage, there is homeostasis. He's right, but the "facts" are morally bankrupt.
Veterans ***who died by suicide were more likely to have sleep disorders, traumatic brain injury, or a pain diagnosis.*** "A study done by the Department of Veterans Affairs discovered that veterans are more likely to develop symptoms of PTSD for several reasons such as:

- Longer times at war
- A lower level of education
- More severe combat conditions
- Other soldiers around them killed
- ***Brain/head trauma***
- Female gender
- Life lasting physical injuries
- Military structure"

Brain/head trauma is the same as Traumatic Brain Injury (TBI) or concussions although there could be actual penetrating head injuries from explosions, hostile fire, etc."[19]

What is the Relationship Between TBI and Suicides?

Our country is currently experiencing a ***20-year epidemic*** of monumental proportions in the form of ***military suicides***. At 20 suicides per day, we have experienced an estimated 109,500 (15 years x 7,300) military suicides since 2005, and the number continues to grow.

"Veterans with multiple brain injuries are twice as likely to consider suicide, compared with those with one or none."[20] A VA site comments: "A new study finds that post 9-11 Veterans with a history of repeated traumatic brain injuries-versus none-are at much greater risk for considering suicide."[21] The study stemmed from interviews with more than 800 Veterans who held combat roles in Iraq and Afghanistan. About half of the Veterans in the study experienced at

[17] The August 3, 2016, VA Suicide Among Veterans and Other Americans 2001-2014 Report, Page 9
[18] The August 3, 2016, VA Suicide Among Veterans and Other Americans 2001-2014 Report, Page 15
[19] The "United States Military Veteran Suicide," article on Wikipedia edited May 5, 2020
[20] Mike Richard, The VA Research News from the U.S. Department of Veterans Affairs reported on November 20, 2018, Study
[21] The VA Research News from the U.S. Department of Veterans Affairs reported on November 20, 2018, Study, the study was funded by the VA's Mid-Atlantic Mental Illness Research, Education and Clinical Center (MIRECC), and appeared online in the journal Psychological Services in November 2018. Dr. Robert Shura, a neurologist at the W.G. (Bill) Hefner VA Medical Center in North Carolina led the study. The study was funded by the VA's Mid-Atlantic Mental Illness Research, Education and Clinical Center (MIRECC), and appeared online in the journal Psychological Services in November 2018. Dr. Robert Shura, a neurologist at the W.G. (Bill) Hefner VA Medical Center in North Carolina led the study.

least one TBI. Of those, almost 20 percent had a history of multiple TBIs reported suicidal ideation, compared with 11 percent with one TBI and 9 percent with no history of TBI. The report also points out that 18 percent met the criteria for major depression disorder (MDD), a significantly related suicide ideation symptom. Roughly 40% reported some level of suicide ideation.

The "Relationship between traumatic brain injury history and recent suicidal ideation in Iraq and Afghanistan era Veterans reports of 838 Iraq and Afghanistan war-era Veterans. Approximately 50% reported a lifetime history of at least one TBI, and 17.9 percent met criteria for current major depressive disorder (MDD)."[22] "The report further states that current depression and poor sleep quality were consistently associated with recent suicide ideation."[23] Increasingly across multiple studies since 2004, TBI has been directly linked to increased suicide ideation amongst Veterans. The current VA treatment protocol for TBI is a symptom-driven non-FDA-approved prescription drug that has continued to produce the same suicide rates for the past 14-years.

"The systematic review and meta-analysis found a 2-fold higher risk of subsequent suicide among more than 700,000 patients diagnosed with a concussion and or mild TBI, compared with more than 6.2 million individuals who had not been so diagnosed."[24] One of the most critical findings from the extensive study review of 17 different studies indicated, "There are several possible mechanisms that may explain the association between concussion and or mild TBI and suicide. A recent meta-analysis of neuroimaging studies of patients with mild TBI reported abnormal activity on functional magnetic resonance imaging and abnormal structural connectivity in brain regions critical for cognitive and emotional processing."[25] We know from our research the VA does not currently recommend imaging in their guidelines for the first 30-90 days of diagnosis. So, the veterans' mTBI is not being diagnosed early or at all through imaging technology (fMRI, SPECT). The report goes on to report, "Our results suggest that compared with people with no history of concussion and or mild TBI, there is evidence of a heightened risk of suicide, suicide attempts and suicide ideation among individuals diagnosed with these conditions."[26]

TBI Veteran suicides have not subsided in any meaningful way since 2005; in fact, they have continued to climb. The VA data beginning in 2018 reflects an average of 6,067 veterans committing suicide per year at a rate of 27.7 per 100,000; that is on average of 352 more per year than 2005 (5,787 to 6,139), and the rate per 100,000 has escalated 7.1 basis points (23.9 to 31.0) (Table 7) from 2005 to 2017. Over 13 years, the number of Veteran suicides per year has escalated 6.1 percent with no signs of improvement. The veteran population has decreased by over 5 million during this period. What is not accounted for in the statistics are Veterans not enrolled in the VA committing suicide. 20 Veteran suicides estimated per day, 7,300 per year represents an estimate of all Veterans inside and out of the VA.

[22] Posted on pubmed.ncbi.nlm.nih.gov on May 16, 2019
[23] Posted on pubmed.ncbi.nlm.nih.gov on May 16, 2019
[24] The American Medical Association 2018 article in the JAMA Neurology, "Association of Concussion with the Risk of Suicide, A Systematic Review and Meta-Analysis
[25] The American Medical Association 2018 article in the JAMA Neurology, "Association of Concussion with the Risk of Suicide, A Systematic Review and Meta-Analysis
[26] The American Medical Association 2018 article in the JAMA Neurology, "Association of Concussion with the Risk of Suicide, A Systematic Review and Meta-Analysis

Our research did not identify the link of how many Veteran suicides were PTSD misdiagnosed or actual TBI Veterans. However, previous industry research has identified a correlation between TBI/PTSD diagnosis and suicides. In our economic analysis, we used 20 Veteran suicides per day, or 7,300 per year, as the basis for identifying the overall state financial impact. The 20 per day number has been widely used and reported throughout the history of the VA until just recently, in 2020. The VA excluded reporting Guard and Reserve suicides along with active-duty numbers, essentially lowering the reporting numbers but not lowering the actual number of suicides occurring across the entire military spectrum.[27]

Estimated 2021 TBI Veteran Suicide Epidemic (VSE) Societal Cost Impact

(A) States	(B) Estimated State Veteran Population See Note 1	(C) Percent of Total US Veteran Population See Note 2	(D) Estimated Veteran Suicides Per Year (C X 7300) Note 3	(E) 2017 Median Household Income See Note 4	(F) 2018 State Tax Rate	(G) State Tax (EXF) See Note 5	(H) Income over $38,701	(I) Federal Tax Rate/ 22% over $38,701+ $4453 See Note 6	(J) Social Security Tax/ 6.2% per employee See Note 7	(K) Medicare Tax/1.45% per employee See Note 8	(L) Total Federal Income Tax Collected (I+J+K))	(M) Total Veterans VSE State Income Tax Impact (D X G)	(N) Total Veterans VSE Federal Income Tax Impact (D X L)	(O) Total Veteran VSE Disability Impact (D X $13,349.16) Note 9	(P) Social Security Disability Payments (D X $14,400) Note 10
Maryland	408,522	2.0%	146	$80,776.00	5.75%	$4,644.62	$42,075.00	$13,709.50	$5,008.11	$1,171.25	$19,888.86	$678,114.52	$2,903,773.56	$1,948,977.36	$2,102,400.00

Table 2

Note 1: 2017 Veteran populations from va.gov/vetdata/veteran_population.asp
Note 2: Individual state percent determined by taking the total veteran population of each state and dividing by total US population of 20,590,510 times 100
Note 3: 20 suicides per day x 365 equals 7,300 per year (August 28, 2019, VA Secretary Wilkie announcement at American Legion National Conference). 2019 VA National Veteran Suicide Prevention Annual Report, Page 3, 16.8 suicides per day in 2017, 2.5 suicides per day for Guard and Reserves equates to 19.3 per day, US Dept of VA, "Suicide Among Veteran and Other Americans 2001-2014" Mentalhealth.va.gov, June 1, 2019.
Note 4: 2017 median incomes from en.wikipedia.org
Note 5: Individual state3 income taxes account for 37% of state tax collections on average. Individual state tax rates from taxfoundation.org, top state marginal personal income tax rates for 2018
Note 6: Federal income tax rate based on 2018 tables and include the following: 22%=$38,701 to $82,500, $4453 plus 22% of the amount over $38,701
Note 7: 2019 Social Security tax based on 6.2% for employee and employer or 12.4% total
Note 8:2019 Medicare tax rate based on 1.45% for employee and employer or 2.9% total

[27] This was a concern in our research as close to 50 percent of the Guard and Reserves were deployed to Iraq and Afghanistan from 2001 through 2018. Reporting this data by states has been dubious and under reported. Consequently, we choose the conservative "20 per day number" as it more accurately reflects the number of military suicides occurring across America in all the active duty, reserves, and guard military services.

Note 9: For disability payments, we assumed 50% disability rating based on the presumption for service connection for all Veterans and states as the average stated by Hill & Ponton Disability Attorneys, 50% disability rating being married, with one child and one parent equates to 2020 VA.gov monthly payment of $1,112.43 per month x 12=$13,349.16 per year per Veteran.
Note 10: www.Militarybenefits.info reported that in 2016 the Social Security Administration (SSA) official site indicated more than 600,000 Veterans received daily payments at a range of $800-$1800 or an average of $1200 per month per Veteran x 12 = $14,400

The toll suicides are having on our Veterans, and their families impose an economic toll that can be calibrated with a higher degree of fidelity than the humanistic toll. The average Maryland economic impact of TBI Veteran suicides per year on lost state and federal taxes is estimated at ***$3,581,888 million per year*** ($678,114+$2,903,773). The VA and Social Security disability annual impact is estimated to be ***$4,051,377 million*** ($1,948,977+$2,102,400). The estimated annual fiscal impact is ***$7,633,265 million per year*** (Table 2). These societal costs do not include prescription medications, hospitalizations, hospital or doctor medical visits, illegal drugs, community services charges, or the failed suicide attempts medical cost each Veteran undertakes each year. Consequently, the economic impact we have identified for suicides is a very conservative estimation.

The lost state income tax, federal income tax, VA, and social security disability payments from managing depression and suicidal ideation are taking their toll on our economy. In 2019, 45,390 Americans committed suicide, of which 6,139 were United States military Veterans – about 13.5 percent. Between 2005 and 2016, the suicide rate for Veterans had risen by 80 percent.

Suicide statistics for the US Veteran population indicate an average of 20 veterans per day committed suicide. Although Veterans account for only 8.5% of the US adult population, they disproportionately represent 17.9% of all deaths by suicide in US adults.[28] Additionally, it has been determined that Veterans receiving high doses of opioid painkillers are more than twice as likely to die by suicide than those receiving low doses.

Researchers with the University of Michigan and with the Serious Mental Illness Treatment, Resource and Evaluation Center, and the Center for Clinical Management Research at the VA Ann Arbor Healthcare System found in 2016 that Veterans receiving the highest doses of opioid painkillers were more than twice as likely to die by suicide, compared with those receiving the lowest amounts. The research team looked at nearly 124,000 Veterans who received VA care in 2004 and 2005. All had non-cancer chronic pain and received prescriptions for opioids. Using the National Death Index, the researchers identified 2,601 patients who died by suicide before the end of 2009.

[28] U.S. Department of Veterans Affairs, 2016

VA Gov Data 2005-2017 Veteran Suicide Deaths

Year	Veteran Suicides	Veteran Population Estimate	Veteran Crude Rate Per 100,000
2005	5,787	24,240,000	23.9
2006	5,688	23,731,000	24.0
2007	5,893	23,291,000	25.3
2008	6,216	22,996,000	27.0
2009	6,172	22,603,000	27.3
2010	6,158	22,411,000	27.5
2011	6,116	22,061,000	27.7
2012	6,065	21,765,000	27.9
2013	6,132	21,415,000	28.6
2014	6,272	21,029,000	29.8
2015	6,227	20,560,000	30.3
2016	6,010	20,170,000	29.8
2017	6,139	19,803,000	31.0
13 Year Total Suicides	78,875	22,005,769	27.7
Total Avg Per Year	6067	Total Average	Total Average

Table 3

Note 1: The data was extracted from files prepared by the Department of Veteran Affairs Office of Mental Health and Suicide Prevention Mentalhealth.va.gov, National Veteran Suicide Date and Reporting Data Appendix - https://www.mentalhealth.va.gov/suicide_prevention/data.asp
Note 2: The VA suicides recorded in Table 3 only include those veterans enrolled in the VA health care system. Approximately 10.2 million or 51 percent of Veterans are not enrolled in the VA, and suicides related to non-VA enrolled veterans were not accounted for in this chart. If you factor in the National Guard and Reserves components, it's another 3.3 suicides per day, and hence the VA estimate of 20 suicides per day or 7,300 per year were used in the cost analysis throughout this report

The US military has lost more troops to suicide than combat over the last two decades. Veterans Affairs Secretary Robert Wilkie informed the American Legion's national conference in Indianapolis on August 28, 2019, "20 Veterans a day kill themselves, about double the rate of the rest of the population". From 2006 through 2014, the DEA.gov website tracks all opioid drugs distributed across the entire US; the VA distributed over 847,000,000 million opioid pills. This accounting was from just 4 of 8 VA Consolidated Mail Outpatient Pharmacies (CMOPs) that account for approximately 80 percent of the prescription medications distributed yearly in the VA system. In Q42012, the VA indicated over **679,000 Opioid Use Disorder (OUD)** Veterans in the VA system. If 679,000 were prescribed opioids, that equates to approximately 155 opioid pills for every OUD Veteran. It was not just the number of opioid medications distributed; the dosage of the pills ranged from 40 to 400 mg per tablet. These high dosage opioid pills were a contributing factor in the 679,000 OUD Veterans.

Secretary Wilkie warned, "the VA can't do it alone, because 70 percent of those Veteran suicides never come to the VA in the first place". Presidential Executive Order on a National Roadmap to Empower Veterans and End Suicide states, "answering this call to action requires an aspirational, innovative, all-hands-on-deck approach to public health- not government as usual. To reduce the

Veteran suicide rate, the Federal Government must work side-by-side with partners from state, local, territorial, and tribal governments, as well as private and non-profit entities." Twenty veterans per day are 7,300 veterans per year, and if 51% are not enrolled in the VA, that is 3,723 Veteran suicides outside the VA medical arena. The number may be under-reported. Many have underlying mental health conditions or substance use disorders aggravated by their military TBIs, increasing their risk. "Research Review on September 2018 Traumatic Brain Injury and Suicide deployment-related TBI, 14.0% to 23.0% screened positive for TBI during their deployment, and almost all TBIs were mild.[29] It's estimated 51 percent of service members deployed to Iraq and Afghanistan were National Guard and Reserves.

The TBI Veteran Opioid Epidemic

Chronic pain is more common in Veterans than in the non-Veteran US population, more often severe and in the context of comorbidities. Pain severity with mental health comorbidities results in high impact pain with a substantial restriction of participation in work, social, and self-care activities. The VHA has found 1 in 5 Veterans report persistent pain, 1 in 10 Veterans say severe constant pain, and 1 in 3 diagnosed with chronic pain.[30] "The most frequently identified risk factor among Veterans who died by suicide was pain."[31] This pain migration leaves most combat Veterans at high risk of opioid medication addiction. The VA/DoD approach for pain management from 2006 through 2017 of prescribing opioid pills to veterans has been devastating. According to data extracted from the DEA website, over 847 million opioid medicines were prescribed and distributed to veterans through the VA Consolidated Mail Outpatient Pharmacies from 2006 through 2014. Data points towards the VA self-inflicting its own Opioid Use Disorder (OUD) over this period by prescribing low and high dosage opioid pills for pain.[32] The long-term economic impact on TBI Veterans is profound. An estimated 25-41% of patients on prescription opioids meet the criteria for Opioid Use Disorder. Although the VA began to make strides in late 2013 through 2017 to reduce the number of veterans being prescribed opioids, the epidemic had already gained a foothold. Veterans were dying at an epidemic rate. The number of veterans on long-term opioid therapy Q4 FY 2012 had surpassed 438,000. <u>There is a strong correlation between this regimented prescription protocol and the instances of TBI veterans succumbing to overdose and or committing suicide during this time.</u> The VA approach to long-term pain management for the symptoms of TBI/PTSD Veterans has escalated into a national opioid and suicide epidemic that, to this day, is continuing with no end in sight.

[29] Terrio, H., Brenner, L.A., Ivins, B.J., Cho, J.M, Helmick, K., Schwab, K., Scally, K., Bretthauer, R. & Warden, D. (2009). Traumatic brain injury screening: Preliminary findings in a US Army Brigade combat team. *Journal of Head Trauma Rehabilitation, 24*, 14-23
[30] Hsrd.research.va.gov, Trends in Veterans Reporting Chronic Pain from 2008 to 2016: A National VA Study, Evan Carey
[31] The Behavioral Health Autopsy Report. 2015
[32] See for example: Art Levine, "How the VA Fueled the National Opioid Crisis and is Killing Thousands of Veterans," NEWSWEEK, October 12, 2017

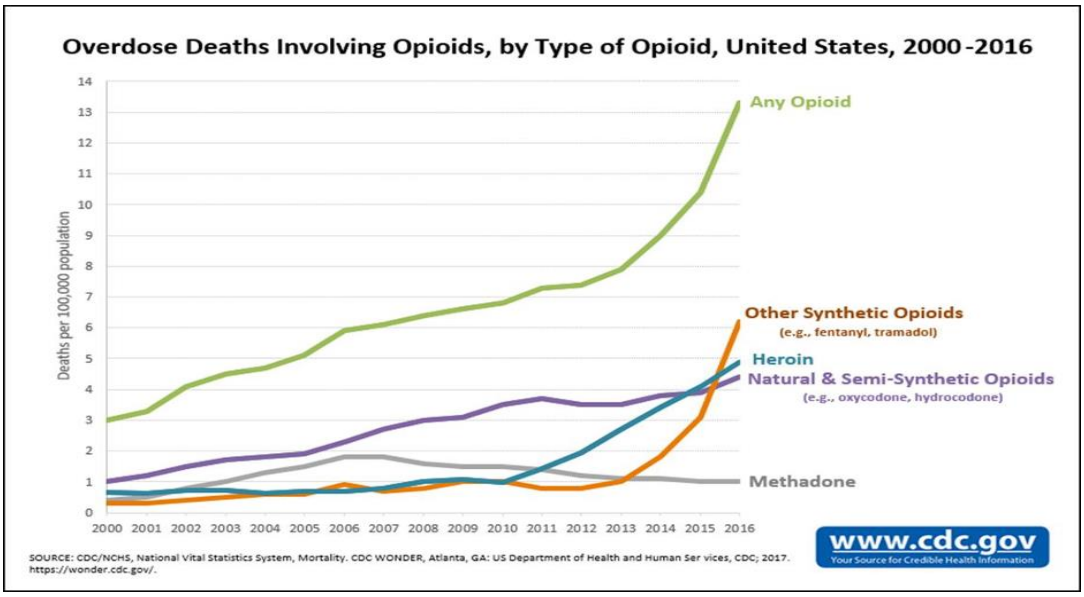


Figure 1

Chart taken from Department of Veteran Affairs, The VA Opioid Safety Initiative-How Did We Get Here and What is Ahead? By Friedhelm Sandbrink, MD and Von Moore, Pharm D, HSRD.research.va.gov

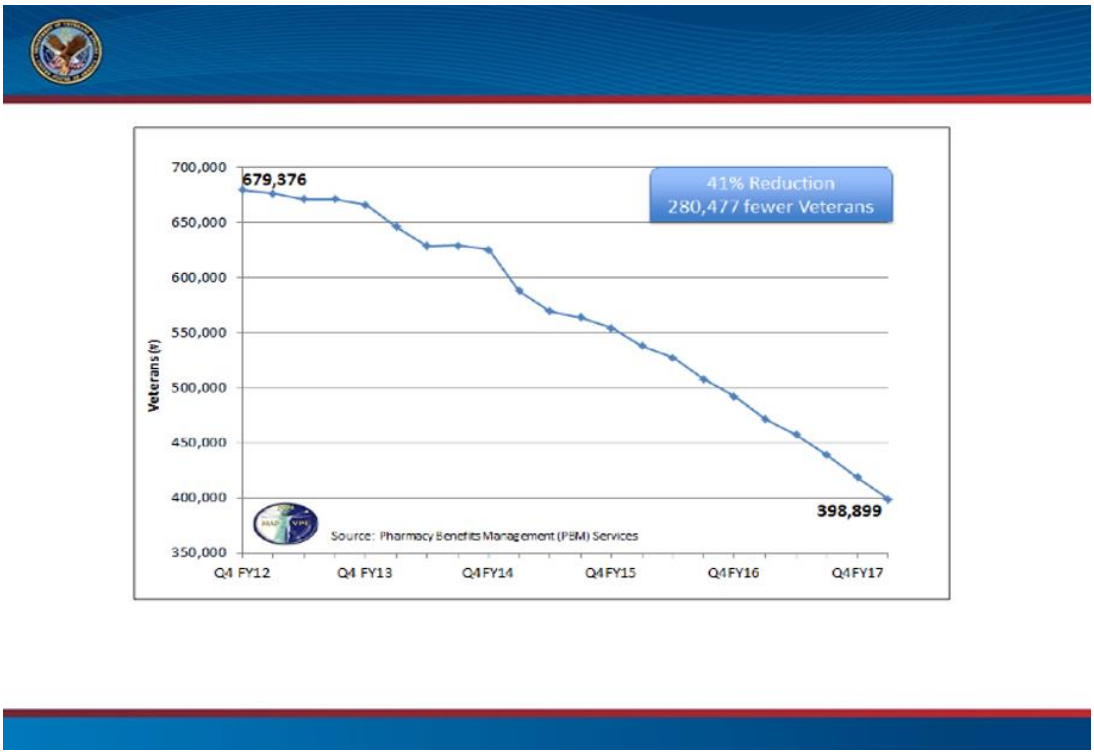


Figure 2

Chart taken from Department of Veteran Affairs, The VA Opioid Safety Initiative-How Did We Get Here and What is Ahead? By Friedhelm Sandbrink, MD and Von Moore, Pharm D, HSRD.research.va.gov

The TBI symptom-based approach by the VA and DoD resulted in many Veterans being either over opioid prescribed for their symptoms or abusing the system in getting the VA and outside medical doctors to prescribe simultaneously. The economic impact had migrated beyond simply the lost tax wage incentive when over 3.5 veterans died daily from OUD.

The Drug Enforcement Administration (DEA) website DEA.gov reflects that over 847,002,681 opioid pills were delivered to the VA from 2006 through 2014, equating to 105,875,335 opioids per year (847,002,681/8). The VA accounting of ***679,376 OUD*** (Figure 2) Veterans in FY Q42012 equates to 156 opioids issued to each OUD Veteran per year. There is a strong correlation between this regimented prescription protocol and the instances of TBI veterans succumbing to overdose and or committing suicide during this time. It is interesting to note, Veterans receiving prescription opioids through the VA CMOP's were simultaneously receiving opioids from their medical doctors outside the VA. There were no checks and balances in place during this time to prevent Veterans from receiving double prescriptions and dosing, further inflaming addictions and suicides with TBI Veterans. Opioid pill distribution to the VA through 2020 could not be identified in our research on the DEA.gov website.

Our conservative estimate is 1,346 Opioid Use Disorder TBI Veterans in Maryland or .33 percent of the state Veteran population (408,522/20,590,510=0.0198% x 68K= 1346 OUD Veterans in Maryland). **The economic impact on state tax revenue is estimated at $6,251,659 and the federal income tax at $26,770,406 per year. When we couple disability payments of $17,967,969 and Social Security payments of $19,382,400 together, it equates to $37,350,369. All total an estimated $70,372,434 yearly economic impact ($6,251,659+$26,770,406+$17,967,969+$19,382,400).** See Table 4 below.

TBI Veteran 2021 Estimated Opioid Use Disorder (OUD) Cost Impact

(A) States	(B) Estimated State Veteran Population See Note 1	(C) Percent of Total US Veteran Population See Note 2	(D) Estimated Veteran Opioid Use Disorder (C X 68K) Note 3	(E) 2017 Median Household Income See Note 4	(F) 2018 State Tax Rate	(G) State Tax (EXF) See Note 5	(H) Income over $38,701	(I) Federal Tax Rate/ 22% over $38,701+$4 453 See Note 6	(J) Social Security Tax/ 6.2% per employee See Note 7	(K) Medicare Tax/1.45% per employee See Note 8	(L) Total Federal Income Tax Collected (I+J+K))	(M) Total Veterans OUD State Income Tax Impact (D X G)	(N) Total Veterans OUD Federal Income Tax Impact (D X L)	(O) Total Veteran OUD Disability Impact (D X $13,349.16) NOTE 9	(P) Veteran Social Security Disability Payments (D X $14,400) Note 10
Maryland	408,522	1.98%	1346	$80,776.00	5.75%	$4,644.62	$42,075.00	$13,709.50	$5,008.11	$1,171.25	$19,888.86	$6,251,659.00	$26,770,406.00	$17,967,969.00	$19,382,400.00

Table 4

Note 1: 2017 Veteran populations from: https://www.va.gov/vetdata/veteran_population.asp

Note 2: Individual state percent determined by taking the total veteran population of each state and dividing by total US population of 20,590,510 times 100
Note 3: 20 suicides per day x 365 equals 7,300 per year (August 28, 2019, VA Secretary Wilkie announcement at American Legion National Conference). 2019 VA National Veteran Suicide Prevention Annual Report, Page 3, 16.8 suicides per day in 2017, 2.5 suicides per day for Guard and Reserves equates to 19.3 per day, US Dept of VA, "Suicide Among Veteran and Other Americans 2001-2014" Mentalhealth.va.gov, June 1, 2019.
https://www.mentalhealth.va.gov/docs/2016suicidedatareport.pdf
Note 4: 2017 median incomes from en.wikipedia.org
Note 5: Individual state3 income taxes account for 37% of state tax collections on average. Individual state tax rates from taxfoundation.org, top state marginal personal income tax rates for 2018
Note 6: Federal income tax rate based on 2018 tables and include the following: 22%=$38,701 to $82,500, $4453 plus 22% of the amount over $38,701
Note 7: 2019 Social Security tax based on 6.2% for employee and employer or 12.4% total
Note 8:2019 Medicare tax rate based on 1.45% for employee and employer or 2.9% total
Note 9: For disability payments, we assumed 50% disability rating based on the presumption for service connection for all Veterans and states as the average stated by Hill & Ponton Disability Attorneys, 50% disability rating being married, with one child and one parent equates to 2020 VA.gov monthly payment of $1,112.43 per month x 12=$13,349.16 per year per Veteran.
Note 10: Militarybenefits.info reported in 2016 the Social Security Administration (SSA) official site indicated more than 600,000 Veterans received daily payments at a range of $800-$1800 or an average of $1200 per month per Veteran x 12 = $14,400

TBI Veteran 2021 Pharmaceutical Economic Impact

The average cost per TBI Veteran for annual prescription cost was determined by escalating the VA quoted 2012 cost of $723 per Veteran per year. We escalated this cost by the US historic yearly inflation rate of 3.24 percent for each year through 2021 to arrive at a conservative estimate of $971 per Veteran per year. With an estimated 17,409 Maryland TBI Veterans,[33] it's estimated to be $16,904,139 annual pharmaceutical cost. If only 49% of the Veterans are enrolled in the VA, it equates to an estimated $8,283,028 annual pharmaceutical cost to the VA ($16,904,139 x 49%) and the remaining $8,621,111($16,904,139 x 51%) to Maryland for subsidized pharmaceutical coverage through Medicare.

Medical examinations entail four main elements, history of symptoms, physical examination, provisional or differential diagnosis, and testing. When long-term pain was identified as a "fifth" element, it appears TBI Veterans were on the receiving end of the pharmaceutical opioid-driven pain management protocol. Veterans reduce approximately 50 percent of their medications after alternative HBOT treatment, and it represents a potential $4,141,514 ($8,283,028/2) economic reduction to the VA CMOP's budget and $4,310,556 ($8,621,111/2) reduction in taxpayer impact annually from Maryland alone. ***Over ten years, that's an estimated $41.4 million ($4,141,514 x 10) financial cost reduction to the VA pharmaceutical budget and $43.1 million ($4,310,556 x 10) to the state of Maryland.***

[33] State Vet TBI Estimate 4.261429% (Rand & VA derived) x 2016 Vet State population (Maryland 408,522) = 17,409

TBI Veteran Economic Tax Impact

TBI Veteran 2021 State and Local Sales Tax Estimated Economic Impact

State	(A) 2019 Sales Tax Rate	(B) 2019 Avg Local Sales Tax Rate	(C) 2019 State Combined Sales Tax Rate	(D) 2017 State Median Household Income	(E) State Tax	(F) Total Federal Taxes (Federal, Social Security, Medicare)	(G) Total Net Income (D-E+F)	(H) 50% Net Income X Combined Sales Tax Rate (C)	(I) State Veteran TBI Estimate	(J) Lost TBI Veteran Sales Tax (H X I)
Maryland	6.00%	0.00%	6.00%	$80,776.00	$2,406.15	$10,207.25	$68,162.60	$2,044.88	17409	$29,373,857.52

Table 5

Note 1: Sales tax sources were Sales Tax Clearinghouse, Tax Foundations calculations, State Revenue Department website
Note 2: Non-table income includes child support, certain Veteran benefits such as disability payments, welfare payments, insurance reimbursements, healthcare benefits, alimony payments
Note 3: State and local sales taxes apply with some exemptions to all goods and specific services to include tobacco, alcohol, certain foods, and motor fuels
Note 4: 411,683 Colorado Veterans x 4.261429% = estimated 17,544 TBI Veterans. State veteran TBI estimate of 4.26% is based on national estimate of 23% TBI of 2.7 million=631K who served in Iraq and Afghanistan. Veterans who served at least twice is 1.5 million x 77%=1,115,000 x 23%=256,450 + 621K=877,450/20,590,510 total US veterans=4.26% of total veteran population by state National estimate of TBI Veterans is 877,450 which was arrived at by 23% X 2.7M service members=631K service members. Two tour Veterans is over half of 2.7M an additional 1.5M service members x 77% (100-23% so we don't double count first group) =256,450 +621K=877,450 TBI Veterans in America/20,590,510 total Veterans=4.26% of total Veteran population are TBI. We applied the 4.261429% x Maryland state Veteran population to get the estimated TBI Veterans in the state.
State sales tax is based on Veterans being gainfully employed and paying taxes on goods and services. **Our estimate is $29.3 million yearly Maryland lost sales tax revenue from TBI Veterans unemployed (Table 5).**

Maryland TBI Veteran 2021 Estimated Homeless and Unemployed Cost

(A) State	(B) 2017 Median Household Income (See Note 3)	(C) 2018 State Tax Rate (See Note 1)	(D) State Tax (C X B) (See Note 1)	(E) Income over $38,701	(F) Federal Tax Rate/ 22% over $38,701+ $4453 (See Note 5)	(G) Social Security Tax/ 6.2% per employee (See Note 6)	(H) Medicare Tax/1.45% per employee (See Note 7)	(I) Total Federal Income Tax Collected (F+G+H)	(J) 2016 Veteran Population (See Note 2)	(K) Estimated 2019 Number of Homeless Vets 37,085 (See Note 4)	(L) State Veteran TBI Estimate 4.261429% X (J) (See Note 8, 8A, 9, 9A)	(M) 2019 State Veteran Unemployment Rate (See Note 8B,)	(N) Unemployed Veterans Per State (J X M)	(O) Homeless Vets Lost State Revenue (D X K)	(P) Homeless Veterans Lost Federal Revenue (I X K)	(Q) TBI Vets Lost Federal Income (I x L)	(R) TBI Vets Lost State Revenue (D x L)	(S) Unemployeed Vets Lost State Revenue (D x N)	(T) Unemployed Vets Lost Federal Revenue (I X N)
MD	$80,776.00	5.75%	$4,644.62	$42,075.00	$13,709.50	$5,008.11	$1,171.25	$19,888.86	408,522	736	17409	0.90%	3677	$3,418,440.32	$14,638,200.96	$346,245,163.70	$80,858,189.58	$17,078,267.74	$73,131,338.22

Table 6
Note 1: Individual state income taxes account for 37% of state tax collections, individual state tax rates from taxfoundation.org top state marginal personal income tax rates for 2018

Note 2: Veteran populations from va.gov/vetdata/veteran_populations.asp
Note 3: 2017 household median incomes from en.wikipedia.org
Note 4: 2019 Veteran homeless data from VA.gov Point-In-Time (PIT) homeless headcount of 37,085 Column K numbers calculated by dividing state Veteran population by the total US Veteran population to attain percent times 37,085
Note 5: Federal income tax rate based on 2018 tables and include the following: 22%=$38,701 to $82,500, $4453 plus 22% of the amount over $38,700
Note 6: 2019 Social Security tax rate based on 6.2% for employee and employer or 12.4% total
Note 7: 2019 Medicare tax rate based on 1.45% for employee and employer or 2.9% total
Note 8: State Veteran TBI estimate of 4.261429% based on national estimate of 23% TBI of 2.7M=621K who served in Iraq/Afghanistan, 2nd tour Veterans 1.5M x 77%=1,115,000 x 23% TBI=256,450+621K=877,450/20,590,510=4.261429%
Note 8A: Estimated 19.5% TBI returning OEF/OIF Veterans + 3.5% (1/2 of 7% with mental health or TBI) =23%, RAND.org, Invisible Wounds, Mental Health and Cognitive needs of Americas Returning Veteran, 2008, Page 2
Note 9: Mild TBI is considered one of the signature wounds of the wars in Iraq and Afghanistan, with as many as 23% of US Veterans who served in these conflicts reporting at least one mTBI during the military service) American Journal of Epidemiology, TBI and Attempted Suicide Among Veterans of Ware in Iraq and Afghanistan, Volume 186, Issue 2, July 15, 2017, Pages 220-226.

If you calculate the estimated Maryland TBI Veterans homeless (736), estimated TBI Veterans total (17,409), and total Veterans unemployed (3,677), it equates to 21,822 (736+17,409+3,677) or approximately 5.34 percent of the total state Veteran population (408,522). **Maryland TBI Veterans state tax revenue loss is estimated to be $80,858,189 annually. The federal income tax loss is estimated to be $346,245,163 or total of $427,103,352 ($80,858,189+$346,245,163). Maryland TBI Veteran homeless state income tax loss is estimated to be $3,418,440 and federal income tax loss of $14,638,200 for total of $18,056,640. The total Maryland state TBI Veteran unemployed state income tax loss is estimated to be $17,078,267 and lost TBI Veteran unemployed federal income loss of $73,131,338 for total of $90,209,605. Total loss from TBI Veteran homeless, TBI Veterans and TBI Veterans unemployed is $535,369,597 ($427,103,352+$18,056,640+$90,209,605) Table 6**

TBI Veteran 2021 Vehicle Property Tax Economic Impact

(A) States	(B) Vehicle Tax Rate	© Annual Taxes on $25K Car	(D) State Veterans with TBI Estimate	(E) Estimated TBI Veterans Non-Car Owners (30%) (D X 30%)	(F) Estimated Annual Loss of Vehicle Taxes TBI Vet Non-Car Owner (C x E)
Maryland	0.00%	$0	17409	5223	$0.00

Table 7
Note 1: Walletbub.com list $24,970 is the value of a Toyota Camry LE four-door sedan as of 2/1/20, the highest-selling automobile in 2019

Note 2: Estimated TBI Veteran non-car owners calculated by taking estimated Maryland TBI Veterans 17,409 x 30% =5,223 and multiplying by estimated tax per vehicle of $0 to arrive at a zero economic impact.

Vehicle ownership is at the core of American employment. Transportation is an essential element for veterans to attain and sustain employment. Dependency on public transportation in many cases may limit the type and location of employment, work hours, and place of domicile
Of the 877,450 estimated TBI Veterans in America, 30 percent equated to an estimated 263,235 Veterans who do not own vehicles. Of the 20,590,510 Veteran total population in America used in our analysis, Veterans not owning cars equated to a mere 1.28 percent of the total population, a very conservative estimation for this cost analysis.

In summary, TBI Veterans who don't own vehicles can be attributed to a combination of issues ranging from; need, type, and amount of prescription drugs, drug and or alcohol-related offenses. In addition, other medical conditions affect the ability to seek and attain a driver's license, i.e., unemployment, homelessness, and suicidal ideation, to name a few. This analysis did not investigate the reasons or number of Veterans not owning vehicles as the focus is conservatively estimating the economic tax impact of non-ownership by TBI Veterans. **Our conservative estimate is zero cost impact for Maryland tax revenue from non-vehicle ownership.**

TBI Veterans 2021 Real Estate Property Tax Loss

(A) State	(B) Real Estate Tax Rate	(C) Annual Taxes on $205K Home	(D) State Veteran TBI Estimate	(E) Estimated OEF/OIF Veterans Home Ownership (D X 34%)	(F) Estimated Annual Loss of Property Taxes TBI Vet Non-Homeowner (C x E)
Maryland	1.09%	$2,235	17409	5919	$13,228,965

Table 8

Note 1: Wallenthub.com depicts $204,900 as the median home value in the US, 2018
Note 2: Column E, 2017 average Veteran homeownership, 18–34-year-olds is 34% as reported in the 2017 American Community Survey
Note 3: Data was not available at the time of this report on the exact number of TBI Veterans who own homes (It is probably more significant than shown)
Note 4: The estimated real estate tax impact of Maryland TBI Veterans was calculated by counting the number of TBI Veterans owning homes times the average annual taxes paid on $205K residence.

We assumed that most veterans leave the service at the state median income levels, especially if they are disabled. Based on the data, we elected to be conservative in our cost assessment and use the US national median home value of $205,000 versus the individual state median home values. The actual 2018 actual home median value was $204,900.

column E of Table 8, the 2017 average Veteran homeownership for 18-34-year-olds is 34 percent based on the 2017 American Community Survey. This is the lowest Veteran age group that reflects homeownership on the survey. This is on the low end of Veteran age groups who own homes and is used as a conservative approach to not overstate the property tax estimate impact on TBI veterans. Second, the 18–34-year-old veteran groups are most likely to be deployed into Iraq and Afghanistan from 2001-2018, most at risk of experiencing TBIs during combat deployments. **Maryland TBI Veteran property tax loss estimate is $13,228,965 annually.**

TBI Veteran 2021 Incarceration Cost Impact

While the prevalence and impact of TBI in the prison population have not been well recognized, its influence is unmistakable.[34] According to the Department of Justice (DOJ) report, approximately 2.3 million people are currently being held in US prisons and jails. Of that number, the rate of TBI is high and ranges from 25% to 87% of incarcerated individuals.[35] In contrast, the rate of TBI in non-incarcerated adults is estimated to be lower than 8.5%.

According to the CDC, "prisoners who have had head injuries may also experience mental health problems such as severe depression and anxiety, substance use disorders, difficulty controlling anger, or suicidal thoughts and or attempts."[36]

At the end of 2019, there were 1,435,500 incarcerated inmates in the US Using 8 percent as Veterans, that is 114,840 total Veterans incarcerated. The CDC indicated that 25% to 87% of inmates in prison experienced a TBI; the average equates to 56 percent. Fifty-six percent of 114,840 is 64,310 veteran inmates estimated with TBI. 64,310 incarcerated TBI Veterans x 2.0% equates to estimated 1,286 TBI Veterans. **Our conservative estimate of Maryland incarcerated TBI Veterans' cost is $51,295,968 per year.**

2015 Maryland State Prison Cost Per Inmate Per Year

(A) States	(B) Prison Poulation	(C) Prison 2015 Reported Expenditures	(D) 2015 Avg Cost Per Inmate (C /B)	(E) 2021 Estimated Avg Cost Per Inmate (D x 3.24% x 5))
Maryland	24,028	$1,071,682,231	$44,601	$52,585.41

Table 9

Note1: Statistics provided https://www.prisonpolicy.org/profiles/CO.html & www.vera.org
Note 2: US historical inflation rate is 3.24%

[34] Slaughter, B., Fann, J.R., & Ehde, D. (2003). Traumatic brain injury in a county jail population: Prevalence, neuropsychological functioning and psychiatric disorders. *Brain Injury*; Wald, Helgeson & Langlois, n.d.
[35] CDC Traumatic Brain Injury in Prisons and Jails, n.d.; Wald et al., n.d.
[36] CDC Traumatic Brain Injury in Prisons and Jails, n.d

Note 3: States not included in the cost per inmate statistics include Maine, Nebraska, New Hampshire, Wyoming, and Mississippi

2021 Maryland Estimated TBI Veteran Incarceration Cost

State	(B) Estimated State Veteran Population Note 2	(C) Percent of Total US Veteran Population	(D) Total Estimated Incarcerated Veterans Per State (C X 64,310)	(E) 2021 Average Cost to Incarcerate Veterans Per Year (D X $39,888)
Maryland	408,522	2.0%	1286	$51,295,968.00

Table 10

Note 1: Veteran population from va.gov.vetdata/veteran_population.asp
Note 2: The cost estimates are based on state and local inmate costs. Federal inmate costs are not included. 2% of 64,310 equals 1,286 estimated Maryland incarcerated TBI Veterans times the national average of $39,888 per inmate per year
Note 3: Maryland average incarceration cost per year extracted from vera.org prison spending in 2015 by state equated to $52,585 escalated at US average inflation rate of 3.24% per year for five years which equates to $61,674 per inmate per year.
Note 4: 64,310 is the estimated total TBI Veterans incarcerated across the US
Note 5: The national estimated average cost to incarcerate an inmate in state prison in 2020 dollars is $39,888 which is taken from 45 state costs and averaged

TBI Veteran 2021 HBOT Estimated Treatment Costs

There is a wide range of hyperbaric oxygen treatment costs based on the facility, civilian or military, private clinic, private or public hospital, or Wound Care Center. Additionally, 13 FDA-approved treatment protocols, each with Medicare or personal insurance coverage rates. Other considerations include the length of procedure time in the chamber and pressure used, the number of treatments required, needed medical assistance pre- and post-treatment, etc. Therefore, we did not attempt to capture all the varying treatment costs across all the variations to estimate total treatment costs for the cost analysis. Instead, we used a flat rate of $250.00 per hyperbaric oxygen treatment hour in mono-place chambers based on varying treatment cost estimates observed and shared from private clinics across the country. The estimated cost per session decreases with economies of scale and when multi-place chambers are used. For example, if 30 people are treated at once in an enormous multi-chamber, the approximate cost is $100 per hour.

The RAND Corporation estimates that in 2010 by investing in more evidence-based treatment, defined as ***"treatments that have been proven to work***, the costs associated with PTSD and major depression would pay for itself within two years. Moreover, those treatments were even without including the costs related to substance abuse, homelessness, family strain, and other indirect consequences of mental health conditions." Brigadier General Richard Thomas may have defined it best, "What's been happening for a long period is that we've been admiring the

problem. But unfortunately, we haven't affected behaviors to get these (soldiers) the treatment they need."[37]

We used an average distribution cost of $250 per hour per hyperbaric oxygen chamber one-hour use as a mean average cost, with an average of 40 (1 Hour) HBOT dives per Veteran, which equates to $10,000 per Veteran ($250 x 40). With an estimated 17, 409 Maryland TBI Veterans, it's estimated to be $174,090,000 for one-time treating 100 percent of the Maryland TBI Veterans. The current annual reoccurring Maryland cost is $584,586,024. On a 40-year reoccurring cost basis to treatment cost, it's less than ¾ of a percent. This approach is a sound financial business case for taking the more economical approach to treating brain injury versus treating with pharmaceuticals over a veteran's lifetime.

Maryland Estimated 2021 Annual Reoccurring TBI Economic Societal Cost

(A) Maryland Estimated Annual TBI Impact Cost for 17,409 Veterans	(B) 10 Year Reocurring Cost Impact (10 X A)	(C) 20 Year Reocurring Cost Impact (20 X A)	(D) 30 Year Reocurring Cost Impact (30 X A)	(E) 40 Year Reocurring Cost Impact (40 X A)
$584,586,024.00	$5,845,860,240.00	$11,691,720,480.00	$17,537,580,720.00	$23,383,440,960.00

2021 Estimated HBOT Treatment Cost as Percent of Yearly Economic Cost

Total Estimated Treatment Cost for 17,409 TBI Veterans	Percent of Treatment Cost to 10 Yr Reocurring Cost	Percent of Treatment Cost to 20 Yr Reocurring Cost	Percent of Treatment Cost to 30 Yr Reocurring Cost	Percent of Treatment Cost to 40 Yr Reocurring Cost
$174,090,000.00	2.97%	1.48%	0.99%	0.74%

Table 11

Conclusion

The data in this report tells a story about the economic impact of TBI veterans in Maryland. The economic impact and the humanistic toll it's having on our TBI Veterans, their families, caregivers are enormous. Calculating these total costs is outside the scope of this document. We did not consider the ripple effect costs in this review. We did not capture social security costs of families needing to enter mental health programs, secondary TBI effects given to wives and children, mental health services in the private sector, family costs to cover accidents, legal fees for divorce, child protection, civil and criminal defense, property dissolution, spouses working as caregivers, etc.

Nevertheless, the available data allows our trusted public officials to understand better the costs of failing to adequately confront the physical damage caused by untreated Traumatic Brain Injuries. Moreover, the fiscal price is only a segment of the total impact on Maryland taxpayers.

[37] http://www.army.mil/-news/2011/05/01/55479-could-be-more-than-a-headache/

"The VA estimates that the 10-year cost of caring for post-9/11 veterans with traumatic brain injury (TBI) alone will are more be $2.4 billion from 2020 to 2029."[38] Historically, TBI Veterans prone than their peers to suffer drug and alcohol dependencies, require caregiver support, or succumb to homelessness or incarceration.

This is not to say all TBI Veterans suffer in the same way. The point is that untreated physical brain injuries, whether diagnosed or not, cause incalculable damage. TBI Veteran costs are continuing to escalate each year substantially. The VA 2021 and 2022 submitted budget proposals reflected just how the cost is escalating every year. VA mental health, suicide, homeless program, suicide, and opioid treatment program budgets alone are escalating at a combined 107.2 percent per year or a 2021 cost of $14.1 billion annually. In any typical business environment, the cost escalation is not sustainable or acceptable. An old tested and tried business approach states, ***"what gets measured gets fixed."*** The cost analysis is designed to bring transparency and allow business discussions on how best to mitigate these enormous cost escalations. The takeaway from this report should be we can treat Maryland TBI Veterans at a fraction of the impact cost and, over a sustained period, see a significant health impact cost reduction and increase in state revenue as a result.

There is a strategic cost as well. Readiness is a term regularly applied to the United States' ability to produce, deploy, and sustain military forces that will perform successfully in combat. Readiness is directly impacted negatively when active-duty service members cannot deploy or are deployed with degraded capabilities such as brain wounds. In our experience, combat veterans who have been exposed to IEDs, concussions, heavy artillery, shoot-room instructing, EOD, high-caliber weapons, and repetitive breaching have endured brain wounding. Since every brain wound is unique, it makes total sense that every combat veteran receives Hyperbaric Oxygenation as part of their rotation, restoration, rehabilitation, just as any weapons system goes through refurbishment.

The highly decorated TBI Veterans below tell their own stories on what path we should follow. The life cycle incurred by too many TBI/PTSD veterans is lamentable. As one Veteran put it: "The cycle is **Deny, Delay, Deceive, Drugs, Depression, and Death, the 6 D's**." A large fraction of our combat veterans sustain invisible injuries; they return home to the DoD and then turn to the VA for help. **The testimonials below of Veterans and their families speak for themselves; we need to listen to their compelling stories of survival and treat them with HBOT.**

[US Army BG **http://tinyurl.com/m97x4jp**]; A VA disability rating is assigned;
[USMC GYSGT **https://bit.ly/2RYqJ4D**]; a round of pharmacology, cognitive, physical, and mental health interventions commence;

[38] Department of Veterans Affairs. (2019). Volume II, *Medical Programs and Information Technology Programs*, p. VHA-150, https://www.va.gov/budget/docs/summary/fy2020VAbudgetVolumeIImedicalProgramsAndInformationTechnology.pdf.

[US Army Major, **http://tinyurl.com/jts2jy3**]; drugs are prescribed;
[USMC and US Army Lt., **https://bit.ly/3foowHU**]; caregiver family support ensues
[MOH recipient **https://tinyurl.com/s67ryzfu;**changing doctors and doses of drugs, including opioids, continue.
[Navy SEAL, **https://youtu.be/kZ3TFGjbptA**]; the Veteran is unemployable
[Mother of Army Sgt, **https://tinyurl.com/y6jaxzbx**]; prescriptions and talk therapy continue
[SGT US Army, **https://youtu.be/DBm3k63Qhkc**]; medication problems ensure
[USAF Ph.D., **https://tinyurl.com/4kp9d9ux**]; hospital and ER visits occur
[SGM USMC, **https://tinyurl.com/wybes8k8**]; marriages disintegrate
[Army Ranger,**http://tinyurl.com/hf3czmw**]; veterans become homeless
[USAF SGT, **https://tinyurl.com/a3f9up73**]; followed, too often by either incarceration or death
[US Army Ranger wife, **https://tinyurl.com/26ayccmy**];

The cost-benefit analysis we developed may have duplicated TBI Veteran head counts throughout the report. Based on the TBI/PTSD cases above, many veterans may have been counted in multiple scenarios to include unemployed, opioid use, pharmaceutical use, suicide ideation, disabled, homeless, incarcerated, and medically retired as described in the report over the decades in the progression of the symptom-based treatment protocol as described by the veteran and family testimonials

RECOMMENDATIONS: What must be done!

Congress must force alignment of spending with brain-wound healing and reduce continual funding of unproven, harmful, and expensive palliatives. Instead, the law and intention must prescribe treatments with scientifically proven data, such as HBOT and other safe and effective therapies. Our solution uses existing medical facilities outside the VA to meet the needs of a medical treatment program for the hundreds of thousands of veterans suffering from brain wounds. Solutions speak directly to the current Executive Branch focus on health care, infrastructure, and efforts to end the suicide and opioid epidemics. Our recommendations include:

1. ***Employ a much less expensive, rapid, and immediately available treatment in HBOT for brain wounds that will produce positive results of "success" within months****. Begin in the seven states (OK, AZ, TX, IN, KY, NC, FL) which have positively addressed the need to Treat the brain-wounded Veterans with Hyperbaric Oxygen Therapy and other Functional Medicine protocols to arrest suicides and heal wounded Veterans. Enact state legislation and fund treatments for your state TBI Veterans and seek reimbursement from the DoD/V.A. for effectively treating the Veterans*

2. ***Request the President and VA Secretary to issue an Executive Order requiring VA Administrators in each VA hospital and clinic to immediately sub-contract out for HBOT services within their communities.*** *HBOT is already an FDA-approved protocol for Diabetic Foot Ulcers (DFU's) and wound-healing treatment (and 14 other medical conditions), so the V.A./DoD requirement for HBOT services is already in place but not currently being deployed. The VA does over 6,000 DFU Lower Limb Amputations*

(LLA's) annually; an estimated 50-70% could be avoided if treated with HBOT. In addition, The VA Mission Act of 2018 funds should be used to provide HBOT for TBI care since the VA does not offer HBOT care for brain wounds. [Ironically, the VA does not have HBOT chambers for Diabetic Foot Ulcers or any other 14 FDA-approved insults even though they are already on the label.

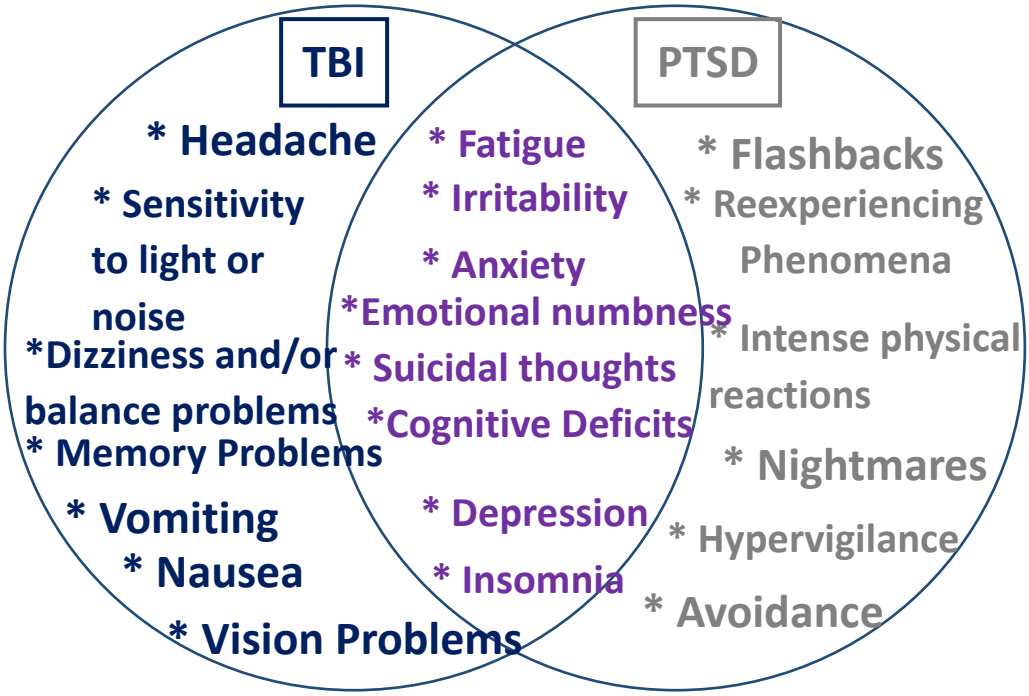
3. ***Private sector infrastructure exists to begin treating brain-wounded veterans immediately.*** *Cost savings in the first year will offset high reoccurring TBI medical costs, as shown in this report. The VA should directly contract with local hospitals and clinics through a national RFP and attain Medicare pricing for HBOT treatments state by state.*

4. **Operational Service Readiness and Preparedness for all the military service branches is a national security priority**. *Unfortunately, readiness is imperiled by TBI and suicides. Suicides among active-duty and veteran service members destroy lives, cost millions of wasted dollars, sap morale, and degrade readiness.* Fifty-one percent of Veterans deployed to Iraq and Afghanistan were Guard and Reserve services. They returned home to their civilian status only to be hindered by TBI/PTSD, directly impacting state tax revenues and medical costs. Treating with HBOT is medically and financially the sound business decision.

5. **There are currently seven states which have enacted HBOT Legislation to treat TBI/PTSD Veterans**. They are OK (HB 1604), AZ (HB1512), TX (HB 271), IN (S.96), KY (HB 64), NC (HB 50), FL (HB 501), and WY (HB Resolution). States should not be required to enact State legislation to care for our TBI/PTSD Veterans. The US Veterans' Bureau War Risk Insurance Act of 1924 allows the Veterans Administration to make provisions to care for our brain-wounded Veterans. National legislation is required to require the VA to treat and fund these treatments for our wounded Veterans. Until it occurs, Governors should enact legislation and seek medical reimbursement from the V.A./DoD through existing enacted legislation.

TBI and PTSD symptoms and their overlap.pdf
Uploaded by: Robert Beckman
Position: FAV

TBI/PTSD/Concussion and Addiction/Withdrawal



Traumatic Brain Injury (TBI) is now recognized as a causative factor for hormonal deficiencies associated with PTSD and personality changes. Psychological, physiological, and physical manifestations in addition to above include: mood swings, bouts of anger, inability to concentrate, learning disabilities, sleep deprivation, increased risk for heart attacks, strokes, high blood pressure, diabetes, loss of libido, menstrual irregularities, pre-mature menopause, obesity, loss of lean body mass, muscular weakness, and a number of other medical conditions that can arise subsequent to head trauma. And notice how alike TBI symptoms are to Concussion and symptoms related to Addiction and Withdrawal.

SB709_Elfreth_FAV.pdf
Uploaded by: Sarah Elfreth
Position: FAV

SENATOR SARAH ELFRETH
Legislative District 30
Anne Arundel County

Budget and Taxation Committee

Subcommittees

Education, Business and Administration

Chair, Pensions

Senate Chair
Joint Committee on Administrative, Executive, and Legislative Review

Joint Committee on the Chesapeake and Atlantic Coastal Bays Critical Area

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March 2nd, 2022

Testimony in Favor of SB709
Post-Traumatic Stress Disorder (PTSD) - Alternative Therapies Fund - Establishment
(David Perez Military Heroes Act (End 22 a Day))

Chairman Guzzone, Vice-Chair Rosapepe, and members of the Budget & Taxation Committee,

I respectfully request a favorable report of Senate Bill 709 to create a fund to provide critical alternative therapies for veterans persevering and surviving with Post-Traumatic Stress Disorder (PTSD).

The incidence of suicide among our veterans and active-duty military personnel have remained at a 20+ constant every day for nearly two decades. Alarmingly, this estimate has only increased within recent years. The suicide rate among active-duty troops has risen from 20.3 deaths-per-100,000 to 28.7 from 2015 to 2020[i]. It is paramount that we support and serve our active-duty service members and veterans now more than ever. Senate Bill 709 calls for the creation of a new fund to support veterans by providing access to meaningful and therapeutic treatments for PTSD.

Over the past decade, the U.S. Department of Veterans Affairs have conducted numerous studies on the relationships between military service, the prevalence of PTSD, and the rate of suicide within these communities. Of these studies, each found a robust correlation between PTSD and suicide for active duty service members and veterans[ii]. Accordng to a recent 2021 joint-report conducted by researchers at Brown and Boston Univeristy, the rate of suicide among active duty service members and post-9/11 veterans is outpacing the suicide rate of the civilian population[iii]. Moreover, the rate at which active-duty personnel and veterans are dying by suicide (a minimum of ~30,177) far outpaces the rate at which service members have been killed in post-9/11 war operations (a minimum of ~7,057) by over 400%. Even more alarming, the U.S. military experienced an 16% increase in the number of recorded suicides from 2019 to 2020[iv].

The use of alternative therapies in the treatment of PTSD in active duty members and veterans has proven to be power tool in combating the ongoing suicide epidemic throughout the U.S. military. It is paramount that the state of Maryland improves access to alternative therapies for PTSD in veterans.

This legislation will:

1. Create the "Post Traumatic Stress Disorder Alternative Therapies Fund" within the Department of Health

2. Allow the fund to be used to support the study of the effectiveness and improving the access to alternative therapies, including hyperbaric oxygen therapy and psychedelics, through providing cost-free access to alternative therapies.
3. Authorize the Department to work with a consortium of organizations on the uses of this fund and the effectiveness of therapies including: The Maryland Department of Veterans Affairs, Johns Hopkins University, University of Maryland, Maryland Sheppard Pratt, and Walter Reed Medical Center.
4. Require a report to the General Assembly on the use of the fund and any other findings.

Legislators across the country are realizing that we must make certain that every available tool is utilized to bring an end to the tragic suicide epidemic that is taking the lives of so many of our veterans. As of this testimony, seven states - including Oklahoma, Texas, Indiana, Kentucky, Arizona, Florida, and North Carolina - have passed critical legislation that provides financial support for veterans seeking alternative treatments for mental and neurological disorders, such as PTSD. Two additional states, Colorado and Idaho, are contemplating similar legislation. This battle will be won one state at a time. Now, it is Maryland's turn to act.

While the debate continues, so does the rate of suicide among our active duty service member and veteran communities. It is time that Maryland join the states listed above by enacting meaningful legislation to provide immediate access to alternative treatments. Our veterans deserve nothing less. By doing so we guarantee that every available tool is being allocated to combat and end the tragic suicide epidemic that continues to take the lives of so many of our veterans.

I respectfully request a favorable report of Senate Bill 709.

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[i] /www.militarytimes.com/news/pentagon-congress/2021/09/30/military-suicides-up-15-percent-in-2020-but-officials-dont-blame-pandemic/#:~:text=The%20suicide%20rate%20among%20active,from%20up%2020.3%20in%202015.

[ii] https://www.ptsd.va.gov/professional/treat/cooccurring/suicide_ptsd.asp#four

[iii] https://watson.brown.edu/costsofwar/files/cow/imce/papers/2021/Suitt_Suicides_Costs%20of%20War_June%2021%202021.pdf.

[iv] https://www.militarytimes.com/news/pentagon-congress/2021/09/30/military-suicides-up-15-percent-in-2020-but-officials-dont-blame-pandemic/#:~:text=The%20suicide%20rate%20among%20active,from%20up%2020.3%20in%202015.

NASW SB 709 Senate Side.pdf
Uploaded by: Sarah Quirk
Position: FAV

NASW, MARYLAND CHAPTER
National Association of Social Workers

Testimony before Senate/House Budget and Taxation Committee
Senate Bill 709: Post-Traumatic Stress Disorder Alternative Therapies Fund- Establishment (David Perez Military Heroes Act (End 22 a Day))

SUPPORT
March 1, 2022

On behalf of the National Association of Social Workers, Maryland Chapter (NASW-MD) Legislative Committee, we would like to express our support for Senate Bill 709 – Post-Traumatic Stress Disorder Alternative Therapies Fund- Establishment.

NASW is the largest national organization of social workers representing over 120,000 social workers and over 16,000 of those are licensed here in the state of Maryland.

The Veteran's Administration is the largest employer of Social Workers in the nation with more than 15,000 Master's degree social workers on staff. Social workers are committed to supporting the health and well-being of our nation's veterans and their families. Veterans have given so much, and in some case, their lives, in service of this country. Approximately 75% of veterans in the U.S. suffer from Post-Traumatic Stress Disorder (PTSD) and veteran suicide rates are at an all-time high and rising.

This fund will support the study of the effectiveness of and improving access to alternative therapies. One of the therapies of focus is 2,4-methylenedioxymethamphetamine (MDMA). In Phase III MDMA trials, funded by the Multidisciplinary Association for Psychedelic Studies (MAPS), 67% of patients no longer met PTSD diagnostic criteria two months after treatment. In comparison, current therapies and medications for PTSD may be needed for a lifetime, diminishing the quality of life for veterans and their families. In addition, MAPS reports that the use of MDMA-assisted psychotherapy for PTSD results in an estimated healthcare cost-savings of more than $103,200 million per patient over a 30-year regular treatment horizon when compared to more traditional treatments.

My grandfather and father are veterans and my twin brother is an active-duty Marine. I have personally witnessed the debilitating effects of PTSD in the veteran population. I have suffered from PTSD most of my life and can personally speak to the life-changing impact alternative therapies have had on such a chronic mental health disorder. For our veterans living with PTSD, the establishment of the PTSD Alternative Therapies Fund would provide supportive research that may one day lead to fuller, healthy, and productive lives.

We appreciate your thoughtful consideration of the benefits of alternative therapies that this program may provide to the men and women who have served this country and ask for a favorable report.

Respectfully,
Emma Earnest UMBC BSW Student, Psychedelic Coach, PTSD Survivor
BSW Representative and CNLI Committee Chair, NASW-MD

5750 Executive Drive, Suite 100, Baltimore, MD 21228
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SB0709 alternative therapies fund.pdf
Uploaded by: Dan Martin
Position: FWA

MENTAL HEALTH ASSOCIATION OF MARYLAND

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Senate Bill 709 Post-Traumatic Stress Disorder Alternative Therapies Fund – Establishment (David Perez Military Heroes Act (End 22 a Day))
Budget and Taxation Committee
March 2, 2022
Position: SUPPORT WITH AMENDMENT

The Mental Health Association of Maryland (MHAMD) is a nonprofit education and advocacy organization that brings together consumers, families, clinicians, advocates and concerned citizens for unified action in all aspects of mental health and substance use disorders (collectively referred to as behavioral health). We appreciate the opportunity to provide this testimony in support of Senate Bill 709 with a friendly amendment.

SB 709 establishes a new fund to support the Maryland Department of Health in studying the effectiveness of and improving access to alternative therapies for post-traumatic stress disorders in veterans. "Alternative therapies" is defined in the bill as including psychedelics, including MDMA, psilocybin, and ketamine.

In 2015, MHAMD launched BrainFutures, a national nonprofit dedicated to improving human outcomes by assessing and advancing practical applications of new scientific understanding of the brain. BrainFutures bring together diverse stakeholders, policymakers, funders, innovators and influencers to accelerate national adoption of effective practices for both brain health optimization and the treatment of mental heath and substance use disorders. Our recent Neurofeedback Report validated the effectiveness of neurofeedback for the treatment of ADHD and anxiety disorders, and our Youth Brain Fitness Report explained why executive function (EF) skills are central to school success, and identified 11 classroom-based EF programs in use in schools across the country that are measurably increasing student academic outcomes.

In early 2021, BrainFutures launched an 18-month psychedelic-assisted therapy initiative to educate policymakers, health care providers, payers and the public about the clinical applications and benefits of psychedelic substances, particularly as relates to mental health issues like post-traumatic stress disorder and treatment-resistant depression. The organization is releasing a series of issue briefs over the next several months and building multi-stakeholder collaborations to prepare for widescale adoption of these treatments and lay a foundation for the regulatory and reimbursement work ahead.

BrainFutures and its cross-disciplinary advisory board of leading experts can provide a wealth of information in the field of psychedelic-assisted therapy that could prove useful in determining how best to responsibly advance these alternative therapies. **Accordingly, we request an amendment to SB 709 to add BrainFutures to the list of organizations the Department of Health shall consult in performing its duties under the bill (pg. 3, lines 15-23).**

SB 709 is an important step in expanding promising new therapies for treating some of the most intractable mental health issues. For this reason, **upon adoption of the amendment outlined above**, MHAMD supports this bill and urges a favorable report.

For more information, please contact Dan Martin at (410) 978-8865

SB 709 Post-Traumatic Stress Disorder Alt Therapie

Uploaded by: Barbara Wilkins

Position: INFO

LARRY HOGAN
Governor

BOYD K. RUTHERFORD
Lieutenant Governor

Maryland
DEPARTMENT OF BUDGET AND MANAGEMENT

DAVID R. BRINKLEY
Secretary

MARC L. NICOLE
Deputy Secretary

SENATE BILL 709 Post–Traumatic Stress Disorder Alternative Therapies Fund – Establishment (Elfreth)

STATEMENT OF INFORMATION

DATE: March 2, 2022

COMMITTEE: Senate Budget & Taxation Committee and Senate Finance Committee

SUMMARY OF BILL:. SB 709 establishes the Post-Traumatic Stress Disorder Alternative Therapies Fund to support the Maryland Department of Health in studying the effectiveness of and improving access to alternative therapies for post-traumatic stress disorder in veterans; and mandates an appropriation to the amount of $1 million in the FY 2024 Budget.

EXPLANATION: The Department of Budget and Management's focus is not on the underlying policy proposal being advanced by the legislation, but rather on the $1 million mandated appropriation provision that impacts the FY 2024 budget.

DBM has the responsibility of submitting a balanced budget to the General Assembly annually, which will require spending allocations for FY 2024 to be within the official revenues estimates approved by the Board of Revenue Estimates in December 2022.

Changes to the Maryland Constitution in 2020 provide the General Assembly with additional budgetary authority, beginning in the 2023 Session, to realign total spending by increasing and adding items to appropriations in the budget submitted by the Governor. The legislature's new budgetary power diminishes, if not negates, the need for mandated appropriation bills.

Fully funding the implementation of the Blueprint for Maryland's Future (Kirwan) will require fiscal discipline in the years ahead, if the State is to maintain the current projected structural budget surpluses. Mandated spending increases need to be reevaluated within the context of this education funding priority and the Governor's tax relief proposals.

Economic conditions remain precarious as a result of COVID-19. High rates of inflation and workforce shortages may be short lived or persist, thereby impacting the Maryland economy. While current budget forecasts project structural surpluses, the impact of the ongoing COVID-19 pandemic continues to present a significant budgetary vulnerability. The Department continues to urge the General Assembly to focus on maintaining the structural budget surplus.

For additional information, contact Barbara Wilkins at (410) 260-6371
or barbara.wilkins1@maryland.gov