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Psychedelic-Assisted Therapy and Psychedelic Science: A Review and Perspective on Opportunities in Neurosurgery and Neuro-Oncology

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Received, July 26, 2022.
Accepted, September 23, 2022.
Published Online, December 8, 2022.

After a decades-long pause, psychedelics are again being intensely investigated for treating a wide range of neuropsychiatric ailments including depression, anxiety, addiction, post-traumatic stress disorder, anorexia, and chronic pain syndromes. The classic serotonergic psychedelics psilocybin and lysergic acid diethylamide and nonclassic psychedelics 3,4-methylenedioxymethamphetamine and ketamine are increasingly appreciated as neuroplastogens given their potential to fundamentally alter mood and behavior well beyond the time window of measurable exposure. Imaging studies with psychedelics are also helping advance our understanding of neural networks and connectomics. This resurgence in psychedelic science and psychedelic-assisted therapy has potential significance for the fields of neurosurgery and neuro-oncology and their diverse and challenging patients, many of whom continue to have mental health issues and poor quality of life despite receiving state-of-the-art care. In this study, we review recent and ongoing clinical trials, the *set and setting* model of psychedelic-assisted therapy, potential risks and adverse events, proposed mechanisms of action, and provide a perspective on how the safe and evidence-based use of psychedelics could potentially benefit many patients, including those with brain tumors, pain syndromes, ruminative disorders, stroke, SAH, TBI, and movement disorders. By leveraging psychedelics' neuroplastic potential to rehabilitate the mind and brain, novel treatments may be possible for many of these patient populations, in some instances working synergistically with current treatments and in some using subpsychedelic doses that do not require mind-altering effects for efficacy. This review aims to encourage broader multidisciplinary collaboration across the neurosciences to explore and help realize the transdiagnostic healing potential of psychedelics.

KEY WORDS: Addiction, Anxiety, Depression, Lysergic acid diethylamide, *N*-methyl-3,4-methylenedioxyamphetamine, Post-traumatic stress disorder, Psilocybin, Psychedelic, Serotonin

Neurosurgery 92:680–694, 2023 https://doi.org/10.1227/neu.0000000000002275

"It does not seem to be an exaggeration to say that psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology and medicine, or the telescope is for astronomy." Stanislav Grof[1]

ABBREVIATIONS: AE, adverse event; **AUD,** alcohol use disorder; **BP,** blood pressure; **CIA,** Central Intelligence Agency; **CSTC,** cortico-striatial-thalamo-cortical; **CT,** clinical trial; **DMN,** default mode network; **DMT,** *N*, *N*-dimethyltryptamine; **ED,** ego dissolution; **HA,** headache; **KAT,** ketamine-assisted therapy; **LSD,** lysergic acid diethylamide; **MA,** meta-analyses; **MDMA,** 3,4-methylenedioxymethamphetamine; **ME,** mystical experience; **N/V,** nausea or vomiting; **OCD,** obsessive-compulsive disorder; **PAT,** psychedelic-assisted therapy; **PFC,** prefrontal cortex; **PTSD,** post-traumatic stress disorder; **SAH,** subarachnoid hemorrhage; **SUD,** substance use disorders; **TBI,** traumatic brain injury; **TMS,** transcranial magnetic stimulation.

After a decades-long moratorium, investigations of psychedelic-assisted therapy (PAT) and psychedelics as neuroplastogens are making a resurgence in behavioral health and neuroscience. Over the last 2 decades, multiple clinical trials with psilocybin, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), and other psychedelics have been completed or are ongoing for patients with depression, anxiety, addiction, post-traumatic stress disorder (PTSD), and terminal illness.[2-6] The results from Phase 2 trials with psilocybin for depression and anxiety and a recent Phase 3 trial for MDMA for PTSD are

promising in both efficacy and safety.[7-11] Functional imaging and clinical investigations with psychedelics are examining neural networks, neural correlates of subjective experience, and the interplay between meditation, contemplative practice, and music.[12-19] The capacity of psychedelics to potentiate neuroplasticity is being explored for stroke, TBI, neurodegenerative disorders, and chronic pain.[20-26]

Considering the massive societal and economic burden of mental illness, the relative ineffectiveness of many current therapies and the transdiagnostic reach of psychedelics, the renewed interest in these plant and fungal medicines, and more recently discovered semi-synthetic and synthetic molecules may offer one of the most impactful developments in the biomedical sciences.[5,20,27,28] This academic fervor is highlighted by the dramatic increase in psychedelic peer-reviewed publications (Figure 1). While recent articles have explored the potential of psychedelics in the psychiatry, palliative care, addiction, and neuropharmacology literature, there are no articles within the neurosurgical and neuro-oncology literature, 2 disciplines largely left outside this resurgence, yet whose challenging patient populations often still need innovative approaches.[3,4,29-31]

This review assesses the state of psychedelic research and offers a perspective on how PAT may help address mental health issues common in neurosurgery and neuro-oncology patients and how psychedelics' neuroplastic potential could benefit other neurosurgical conditions, while also reviewing potential adverse consequences and safety issues surrounding PAT. We focus on psilocybin, LSD, and MDMA (all currently non-US Food and Drug Administration (FDA)–approved Schedule 1 psychedelics) and discuss ketamine because it is currently the only FDA-approved drug with psychedelic properties available to mental health providers for off-label use outside clinical trials.[32]

NOMENCLATURE

Three terms most often used for plant, fungal, and synthetic medicines that can occasion nonordinary states of consciousness are *psychedelic*, meaning "mind manifesting;" *entheogen*, meaning "accessing the divine within;" and *hallucinogen*, meaning "wandering in mind."[29,30] In this study, we use "psychedelic" because it is believed to best capture the essence of what these medicines can elicit. Classic

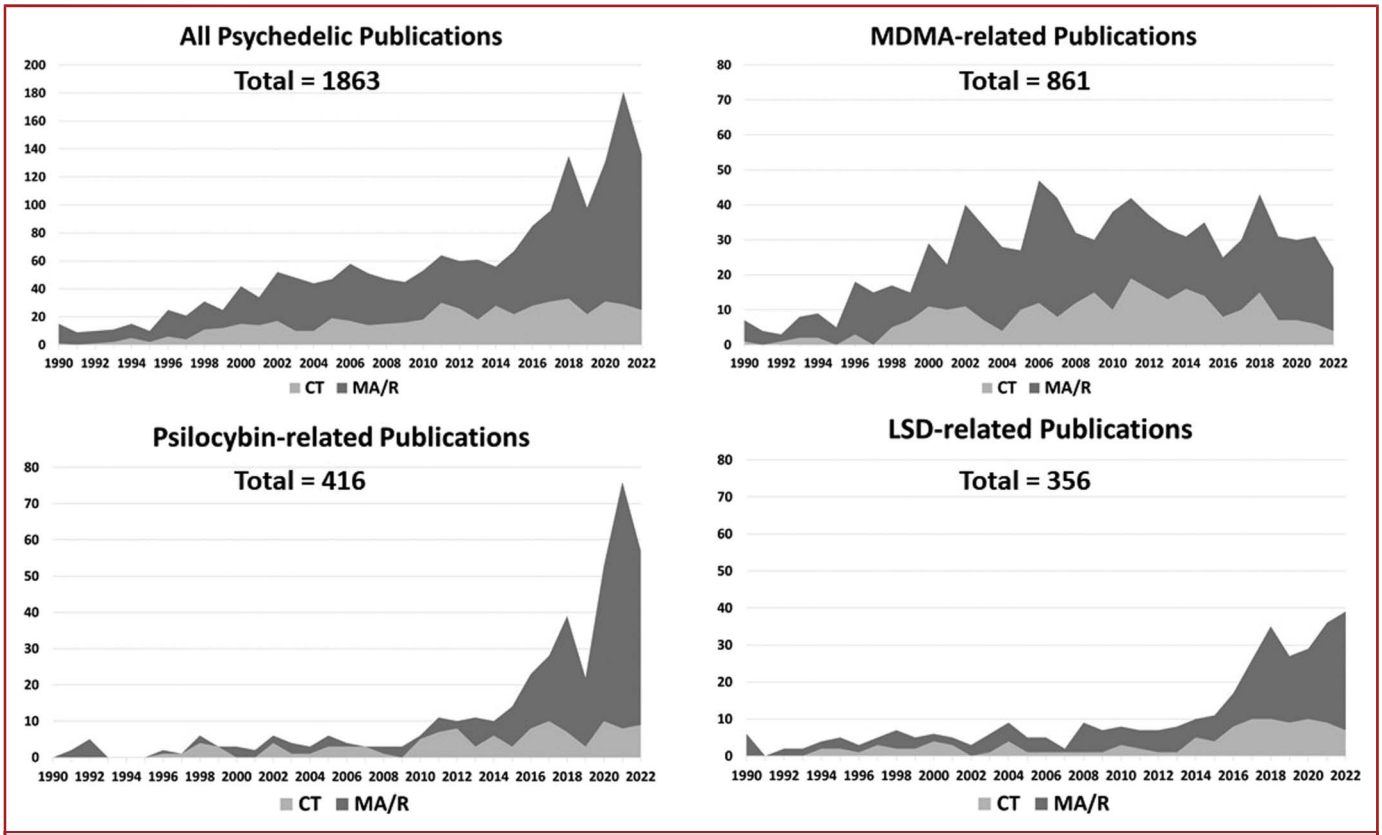

FIGURE 1. *Peer-reviewed publications in psychedelic science from 1990 through June 2022: The four graphs show over the last 3 decades an initial slow then rapid rise in articles focused on clinical applications of all psychedelics, MDMA, psilocybin, and LSD. Publications are shaded to distinguish between CT results or MA and R (Methodology: PubMed was searched using the terms: psychedelic, clinical trial, LSD, 3,4-MDMA, and psilocybin for both human and animal investigations.). CT, clinical trial; LSD, lysergic acid diethylamide; MA, meta-analyses; MDMA, 3,4-methylenedioxymethamphetamine; R, reviews.*

psychedelics include fungal-based psilocybin, semisynthetic LSD, plant-based *N,N*-dimethyltryptamine, and cactus-based mescaline; all are predominantly serotonin 2A receptor (5-HT_{2A}R) agonists and occasion similar kinds of nonordinary experiences.[33] Synthetically produced MDMA is considered an atypical psychedelic that occasions empathy and emotional openness; the terms *entactogen* and *empathogen* are used to describe its effects. MDMA triggers synaptic release of serotonin and other monoamine neurotransmitters, as well as increases in oxytocin, cortisol, and prolactin.[29,34] Ketamine, a dissociative anesthetic, occasions a different nonordinary state of consciousness in subanesthetic doses from the classic psychedelics or MDMA and thus can be considered an atypical psychedelic. It is predominantly an N-methyl-D-aspartate-glutamate-receptor antagonist and currently used off-label in subpsychedelic doses to treat depression and other mood disorders and in PAT at higher subanesthetic doses.[30,32,35]

BRIEF HISTORICAL CONTEXT

Naturally occurring psychedelics including psilocybin-containing mushrooms, mescaline-containing cacti (peyote and San Pedro), and *N,N*-dimethyltryptamine-containing ayahuasca brew have been used in shamanic cultures in some instances for more than 5000 years in healing and other ritual ceremonies.[36,37] The modern era of psychedelics arguably began with Arthur Heffter, a German pharmacologist who in 1897 isolated mescaline as the psychotropically active alkaloid in peyote.[33] Perhaps more important was the serendipitous discovery of the powerful psychotropic effects of LSD by Swiss chemist Albert Hofmann in 1943 and isolation of psilocybin as the psychotropically active alkaloid in magic mushrooms in 1958 by Hofmann et al[33,38,39] (Figure 2). Chemist Alexander Shulgin and his wife Ann synthesized and tested multiple new psychedelic compounds during the 1960s and 1970s, including a revised synthesis of MDMA in 1976, and published many of their observations in academic journals.[40] From the early 1950s with LSD, and late 1950s with psilocybin, PAT for depression, anxiety, and alcoholism was practiced across North America and Europe with hundreds of clinical studies involving thousands of patients.[28,41] However, amid widespread and rapidly increasing use of LSD and psilocybin beyond the confines of clinical care and academic institutions, and perceived counterculture threat, the US Congress passed the Controlled Substances Act in 1970 placing all psychedelics into Schedule I, effectively stopping all clinical research for the next 2 decades.[38,39,41,42]

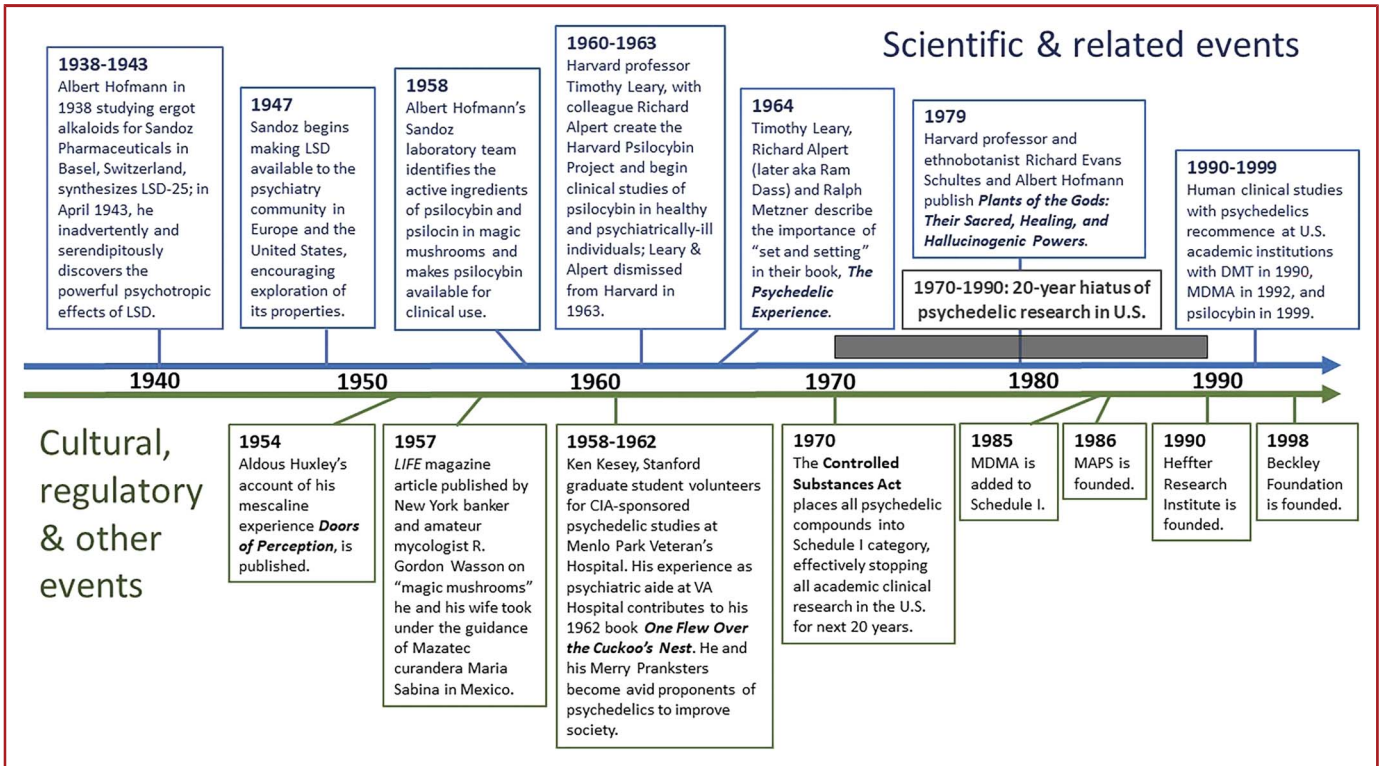

FIGURE 2. *Timeline of pivotal events and people in psychedelic history 1938 to 1999: Beginning with Albert Hofmann's synthesis of LSD-25 in 1938 and ending in the 1990s with the recommencement of psychedelic clinical studies in the United States and Europe, landmark scientific, cultural, and regulatory events and key individuals are noted. For more in-depth historical accounting of these and other pivotal events and people, readers are referred to these references:[36,38-44]. CIA, Central Intelligence Agency; DMT, N, N-dimethyltryptamine; LSD, lysergic acid diethylamide; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-methylenedioxymethamphetamine.* © *Pacific Neuroscience Institute Foundation, 2022. Used with permission.*

MDMA was added to Schedule I in 1985.[43] Despite the Controlled Substances Act, the belief that PAT held great potential for contributing to well-being endured and work was pursued by intrepid scientists, practitioners, and advocates, eventually leading to the current resurgence in psychedelic studies.[28,44]

CLINICAL TRIALS WITH PSILOCYBIN, LSD, AND MDMA

A current search of the National Institutes of Health-maintained database (clinicaltrials.gov) yields 100 clinical trials for psilocybin (21 completed), 21 for LSD (12 completed), and 67 for MDMA (40 completed). Table 1 summarizes actions and targets of these Schedule 1 psychedelics and ketamine.

Psilocybin

Studies of psilocybin-assisted therapy have focused on depression and anxiety, existential distress, and substance use disorders (SUD). Recent trials are targeting demoralization, grief, anorexia, obsessive-compulsive disorder (OCD), headache, and fibromyalgia. The 2 largest randomized double-blind Phase 2 trials for patients with cancer with anxiety and/or depression were conducted at Johns Hopkins (N = 51 subjects) and New York University (N = 29 subjects); 6 months after a single psilocybin session, preceded and followed by supportive psychotherapy, 60% to 80% of subjects had durable reductions in anxiety and/or depression.[9,11] Notably, in these 2 studies, at 6 months after psilocybin-assisted therapy, 67% to 70% of subject rated their psilocybin experience as one of the "top 5 most meaningful of life" and 52% to 70% as one of the "top 5 most spiritually significant of life."[9,11] Similar promising results were shown by the same groups in pilot studies for nicotine addiction and alcohol use disorder (AUD); a recent larger placebo-controlled trial (N = 95) for AUD showed a significant decrease in heavy drinking days over 32 weeks of follow-up.[45-47] The FDA designated psilocybin a "breakthrough therapy" for treatment-resistant depression in 2018 and for major depressive disorder in 2019. Currently, 2 randomized placebo-controlled Phase 2 trials for depression have completed enrollment for treatment-resistant depression and major depressive disorder, and Phase 3 trials are soon getting underway for both indications.

LSD

Studies in healthy subjects have focused on neuroplasticity and comparison with other psychedelics, while treatment studies are assessing utility for anxiety, depression, and cluster headache.[14,17,38,48,49] The fewer LSD trials likely reflects residual stigma of LSD as a counterculture drug and duration of an LSD journey averaging 8-12 hours (compared with 4-6 hours for psilocybin), making the treatment model more demanding on staffing and resources. Nonetheless, given similarities between psilocybin and LSD, future LSD trials for mood disorders and addiction are likely.[49]

MDMA

Studies have focused on PTSD (6 completed Phase 2 trials, 1 completed Phase 3 trial), demonstrating strong efficacy and safety across all types of severe PTSD.[2,10] In the recent Phase 3 trial, after 3 MDMA psychotherapy sessions (18 weeks postbaseline) combined with psychotherapy, 28/42 (67%) of participants in the MDMA group no longer met criteria for PTSD, compared with 12/37 (32%) of those receiving placebo.[10] Should the second Phase 3 trial yield similar results, FDA approval of MDMA-assisted therapy for PTSD is likely. Other therapeutic targets being studied with MDMA include anxiety, eating disorders, and AUD.

SET AND SETTING MODEL OF PSYCHEDELIC-ASSISTED THERAPY

The "set and setting" PAT model, established in the 1960s with its roots in shamanic cultures, is currently part of all clinical trial models and is designed to achieve a transformative yet safe patient experience (Figure 3).[50,51] *Set* refers to the mindset of the patient as informed by the current state of mind and one's life history. *Setting* refers to the environment in which the medicine session or "journey" occurs including the physical space, the music, and the guides.[50,52,53] Patient preparation with psychological counseling occurs over several sessions with trained guides (typically a male and female dyad).[54] A sense of trust, safety, and expectations is established, and the subject reflects on their life history and intentions while developing an attitude of fortitude and curiosity about the coming journey. A mantra often encouraged is "*trust, let go, be open*." The journey which lasts several hours takes place in a comfortable room with appropriate art and lighting, the patient reclining on a bed or sofa with eyeshades; music is of a new age or classical genre, evocative and nonlyrical that builds to support the internal journey and help achieve a peak experience.[50,52-54] Confronting challenging material may lead to profound and beneficial psychological change. In many journeys, particularly with psilocybin and LSD, the patient will have what is termed a mystical experience.[49,53,55]

SAFETY, POTENTIAL ADVERSE EVENTS, AND ETHICAL ISSUES

The requirements to conduct clinical trials with non-FDA–approved investigational Schedule 1 psychedelics such as psilocybin, LSD and MDMA are rigorous. An MD must be on site and readily available, as well as a clinical psychologist both trained in PAT. The other guides can be other health care providers (eg, registered nurses, physician assistants, nurse practitioners, marriage and family therapists) who have undergone PAT training such as provided by California Institute of Integral Studies or Multidisciplinary Association for Psychedelic Studies. Given the powerful nature of the psychedelic experience and the vulnerable psychological state patients

TABLE 1. Overview of Neurohormonal Targets, Acute Actions, and Potential Adverse Events of Psilocybin, LSD, and MDMA in PAT Clinical Trials and Ketamine in KAT Clinical Practice

Drug and DEA schedule	Therapeutic dose range and route	Main neurotransmitter effects	Main hormonal effects	Hemodynamic effects and other systemic AEs or side effects	Duration of effect; number of doses over time	Major clinical indications	Other potential indications	Main cognitive and perceptual effects	Main emotional effects: positive and negative	Mystical experience and ego dissolution	ME and ED predictive of efficacy
Psilocybin Schedule 1 In Phase 2 trials	20-30 mg oral	Serotonin (5HT-2A), Dopamine (partial)	Mild or moderate rise in cortisol, prolactin at higher doses	Mild increase in BP and pulse; pupil dilation, loss of appetite. In minority: N/V, headache, tremulousness, and/or fatigue in some	4-6 h; 1-2 sessions separated by 4-6 wk	Depression, anxiety, distress of terminal illness and cancer, AUD	Grief, nicotine and opioid addiction, OCD, anorexia	Moderate to strong visual hallucinations, audio-visual synesthesias, alterations of space and time	**Positive:** Sense of well-being, empathy, openness, and trust; **negative:** anxiety, fear, and/or paranoia, suicidal ideation in minority	ME and ED in large minority or majority at higher doses	Yes
LSD Schedule 1 In Phase 2 trials	100-250 μgm oral	Serotonin (5HT-2A)	Mild or moderate rise in cortisol, prolactin, oxytocin at higher doses	Mild increase in BP and pulse; pupil dilation, loss of appetite; in minority: N/V, headache and/or fatigue	8-12 h; 1-2 sessions separated by 4-6 wks	Anxiety, depression, cluster headache	AUD, nicotine and opioid addiction	Moderate to strong visual hallucinations, audio-visual synesthesias, alterations of space and time	**Positive:** Sense of well-being, empathy, openness, and trust; **negative:** anxiety, fear, and/or paranoia in minority	ME and ED in large minority or majority at higher doses	Yes

TABLE 1. Continued.

Drug and DEA schedule	Therapeutic dose range and route	Main neurotransmitter effects	Main hormonal effects	Hemodynamic effects and other systemic AEs or side effects	Duration of effect; number of doses over time	Major clinical indications	Other potential indications	Main cognitive and perceptual effects	Main emotional effects: positive and negative	Mystical experience and ego dissolution	ME and ED predictive of efficacy
MDMA Schedule 1 In Phase 3 trials	80-180 mg oral	Serotonin (5HT-2A) Dopamine Norepinephrine	Significant rise in oxytocin; modest increase in cortisol, prolactin	Modest increase in BP and pulse; transient and mild/moderate muscle tightness, loss of appetite, nausea, hyperhidrosis, and/or feeling cold	4-6 h; 3 sessions separated by 4 wks	PTSD	Anxiety, depression, AUD, anorexia, and other eating disorders	Mild visual and auditory perceptual changes; no hallucinations	**Positive:** Reduced fear and anxiety, sense of well-being, increased trust and empathy; **negative:** anxiety and/or distrust, hostility, and/or suicidal ideation in minority	ME and ED in minority	No
Ketamine Schedule 3 Off-label use	0.5–1.5 mg kg IV or IM	NMDA-glutamate receptor antagonist	Mild increase in cortisol and prolactin	Mild increase in BP; N/V in minority	1-2 h; 4-8 sessions over 4-6 wks	Depression, anxiety, PTSD	OCD, SUD	Vivid imagery, derealization, disembodiment, impaired control and vigilance	**Positive:** Sense of unity, openness; **negative:** anxiety, agitation in minority	Variably at higher doses	Mixed results

AE, adverse event; AUD, alcohol use disorder; BP, blood pressure; ED, ego dissolution; KAT, ketamine-assisted psychotherapy; ME, mystical experience; NMDA, N-methyl-D-aspartate; N/V, nausea or vomiting; PTSD, post-traumatic stress disorder; SUD, substance use disorder (relevant references[7-11,29,32,34,35,38,47,49,66]).

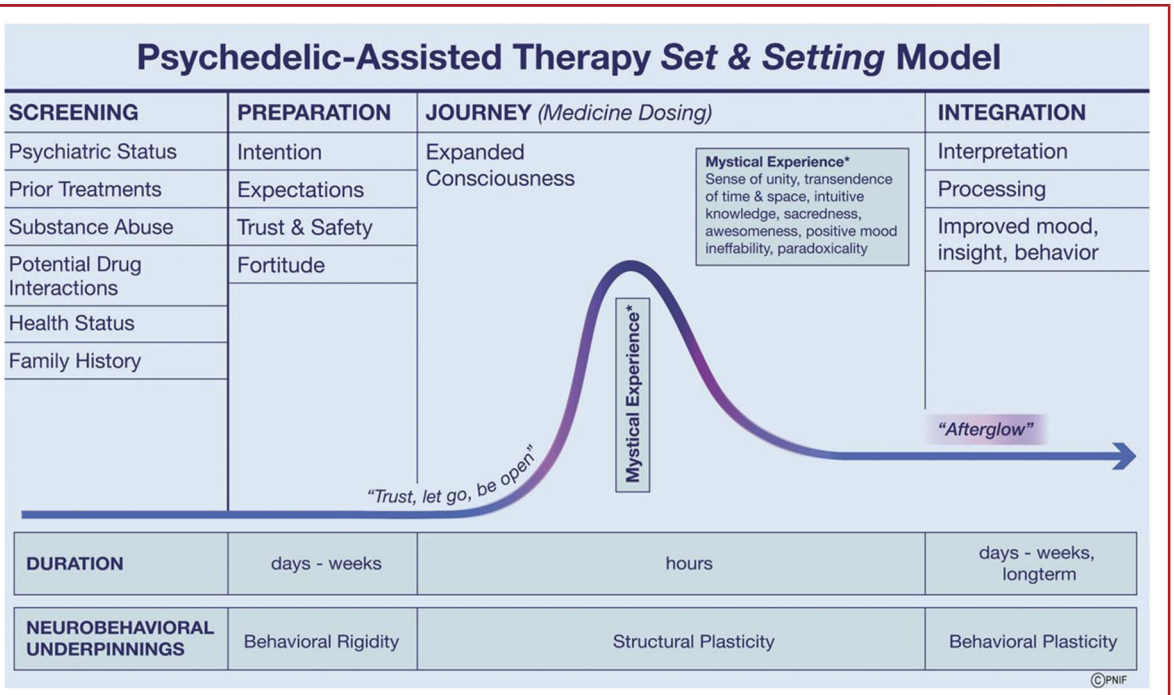

FIGURE 3. *Psychedelic-assisted therapy is akin to a surgical procedure, the success and safety of which depends on experienced guides, patient screening and preparation, an optimized "set and setting," safety protocols, and rigorous postjourney psychological counseling (integration).*[50,54] *Depicted are the phases in current clinical trials of patient screening, preparation, journey, and integration. After detailed patient screening for appropriateness of participation and exclusion criteria, preparation with psychological counseling occurs over several sessions in the days or weeks before the medicine session. The first integration session occurs the day after the journey, in the so-called "afterglow" period followed by subsequent sessions over weeks in which the patient strives to integrate the experience into their life and favorably alter their behavior and outlook.*[53] *For example, a dying individual may find meaning and resolution leading to long-term reduction in demoralization, hopelessness, and death anxiety, resulting in improved quality of life and of death.*[17,68] *The neurobehavioral and structural underpinnings of the transformative process that may occur with PAT are postulated to result from the neuroplastogenic properties of psychedelic medicines.*[20,30,61,70] *PAT, psychedelic-assisted therapy. Adapted from Majic et al.*[53] *© Pacific Neuroscience Institute Foundation, 2022. Used with permission.*

enter during and in the initial days postjourney, having well-trained guides especially in understanding and managing the spectrum of emotional and perceptual responses to psychedelics is essential.[54] With experienced and skilled guides and a well-prepared patient, PAT is typically deeply meaningful, albeit at times challenging. The risk of a "bad trip" is low, and hallucinogen-persisting perceptual disorder is rare.[50,53] Serotonin toxicity has not been reported in clinical trials to date, although most trials have excluded coadministration of psychedelics with serotonergic medications such as antidepressants.[56] As recently emphasized, as such trials and treatments move forward, psychedelic practitioners must adhere to the highest ethical standards focused on patient safety and well-being and embrace a rigorous system of peer review and supervision.[50,54,57]

From a physiological perspective, the classic psychedelics and MDMA are notable for their high safety profile and low addictive potential.[50,58] As detailed in Table 1, psilocybin and LSD cause mild-to-moderate elevations in blood pressure, pulse, and respirations, while MDMA can cause modest increases in blood pressure; all 3 are at the low end of the Harms Scale compared with alcohol, heroin, and cocaine.[9,10,49,58]

In modern clinical trials of psilocybin, LSD, and MDMA using the "set and setting" paradigm, there have been few serious adverse events, largely because of safety guidelines, and careful patient screening, excluding those with a personal or family history of mental illness with psychotic potential such as schizophrenia and bipolar disorder.[7,9-11,49,50] In 7 of the most recent randomized placebo-controlled trials for high-dose psilocybin, LSD, or MDMA (total N = 249 patients), there were no serious medical or psychiatric adverse events reported.[7-11,47,49]

MECHANISMS OF ACTION AND DURABILITY OF PSYCHEDELICS

One of the fascinating questions surrounding psychedelics is how they work and what brain changes are induced long-term.[59-61] How can 1, 2, or 3 psychedelic journeys, accompanied by psychotherapy, lead to months or even years of durable behavioral change? Based on multiple neuroimaging studies, the most widely accepted mechanism of action is that by stimulating 5-HT_{2A}

receptors, the classic psychedelics (psilocybin and LSD) loosen processes that normally act to constrain neural systems involved in cognition, perception, emotion, and sense of self.[5,12,16,17,59,60,62] Three leading models have emerged as to how the classic psychedelics alter neural circuitry leading to this neuroplastic state: the cortico-striatial-thalamo-cortical model,[12,16,61,63,64] the "relaxed beliefs under psychedelics" model,[5,60,65] and the cortico-claustro-cortical model.[12,59] To varying degrees, all 3 models involve the medial prefrontal cortex, posterior parietal and sensory cortices, and other subcortical structures; they all implicate increased excitability of pyramidal neurons in the prefrontal cortex (PFC), leading to dampening of cortical rhythmicity and disruption of large-scale networks such as the default mode network and reduced segregation between networks (Figure 4A).[12,16,59-61]

While the neural underpinnings remain to be clarified, the psychedelic-induced state seems to allow one to recollect and process deep autobiographical information, achieve new understandings of one's self and relationships with others, and gain greater appreciation of one's place within the cosmos.[5,61,62] This state is closely linked to the concept of "mystical experience" which in multiple studies with classic psychedelics predicts therapeutic efficacy.[9,11,45,47,55] "Ego dissolution" is another term used to describe a loss of the usual sense of self as separate entity.[13] The quality and degree of psychedelic-induced ego dissolution and mystical experience are typically measured in clinical trials with validated psychometric instruments such as the 5-Dimensional Altered States of Consciousness Questionnaire and the Mystical Experience Questionnaire.[9,11,45,47,49,55,61]

With MDMA-assisted therapy, a mystical experience and ego dissolution are less often achieved and may not correlate with efficacy.[66] MDMA triggers synaptic release of serotonin, norepinephrine, and dopamine and elevations of oxytocin, cortisol, and prolactin, acting predominantly in pathways involved in emotional and memory processing including the PFC, amygdala, hippocampus, and insular cortex[34,66] (Figure 4B). Increased connectivity between the amygdala and hippocampus, reduced insula activation, and reduced medial PFC connectivity to the amygdala augmented by increased oxytocin, and cortisol levels are hypothesized to facilitate one's ability to reevaluate traumatic events without fear and anxiety, allowing a favorable reorganization of such memories.[4,34]

Ketamine has been shown in a nonpsychedelic model of subanesthetic IV dosing to reliably produce rapid but short-lived relief of depression and suicidal ideation.[32] Since the early 1970s, ketamine has also been known to occasion a potentially therapeutic nonordinary state of consciousness. More recently, an effective ketamine-assisted therapy (KAT) model for depression has been developed using intramuscular, sublingual, or intranasal dosing.[35] KAT seems to result in a dose-dependent "time-out" from usual mind negativity, often a dissociative state in which one feels a separation from their body, intense visions, and even what has been called a near-death experience.[35] Neuroimaging studies suggest this experience results from ill-defined interactions on the PFC, anterior and posterior cingulate cortex, and subcortical structures including the putamen, thalamus, amygdala, and hippocampus.[32,67] Importantly, ketamine has abuse and addiction potential.[32,35]

The durability of PAT with sustained resolution of symptoms seen in recent clinical trials of psilocybin and MDMA and depicted in Figure 3 [9-11,68,69] is likely related to multiple factors that may include psychedelic-induced synaptogenesis and neurogenesis, upregulation of plasticity-promoting genes in the PFC and hippocampus, and of brain-derived neurotrophic factor, mammalian target of rapamycin, and other neurotrophins.[20,30,34,70] Classic psychedelics and ketamine trigger neuritogenesis and synaptogenesis in *in vitro* and *in vivo* models.[20,26,71] It has been proposed that ketamine, using N-methyl-D-aspartate-glutamate receptor antagonism, and the classic psychedelics, using 5-HT_{2A}R agonism, cause similar downstream changes: a glutamate surge, activating PFC pyramidal neurons to release brain-derived neurotrophic factor and mammalian target of rapamycin, which in turn upregulate neuroplasticity genes promoting synaptogenesis and "adaptive rewiring" leading to lasting behavioral and mood improvements.[70]

Thus, PAT with only 1 or few medicine sessions offers a paradigm shift for treating mental health issues, sharply diverging from the daily pharmacopeia approach commonly practiced today. Instead of blunting or suppressing negative thoughts and emotions, these medicines seem to facilitate an expansive psychospiritual approach, allowing deep personal exploration, promoting structural neuroplasticity, and connectivity that may underlie their durability of effect.

POTENTIAL APPLICATIONS OF PSYCHEDELICS IN NEUROSURGERY AND NEURO-ONCOLOGY

Several patient groups may benefit by leveraging (1) the psychedelic properties to heal the mind using PAT and/or (2) the neuroplastic properties to heal the brain (Figure 5). These "mind-altering" and "brain-altering" approaches may overlap and, in some disorders, could potentially be combined with existing treatments such as neuromodulation techniques including deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and stem cell therapies.[72-75]

MOOD DISORDERS AND ADDICTION

As shown in Table 2, potential targets for PAT are the depression, anxiety, and SUD that are common, under-reported, and often undertreated in patients with brain tumors, stroke, SAH, TBI, spinal cord injury, chronic spinal disability, other pain syndromes, and Parkinson disease.[3,4,76-104] For example, psilocybin-assisted therapy may help some of these patients gain greater acceptance of their disability, reduce apathy, and promote living more fully.[82,83]

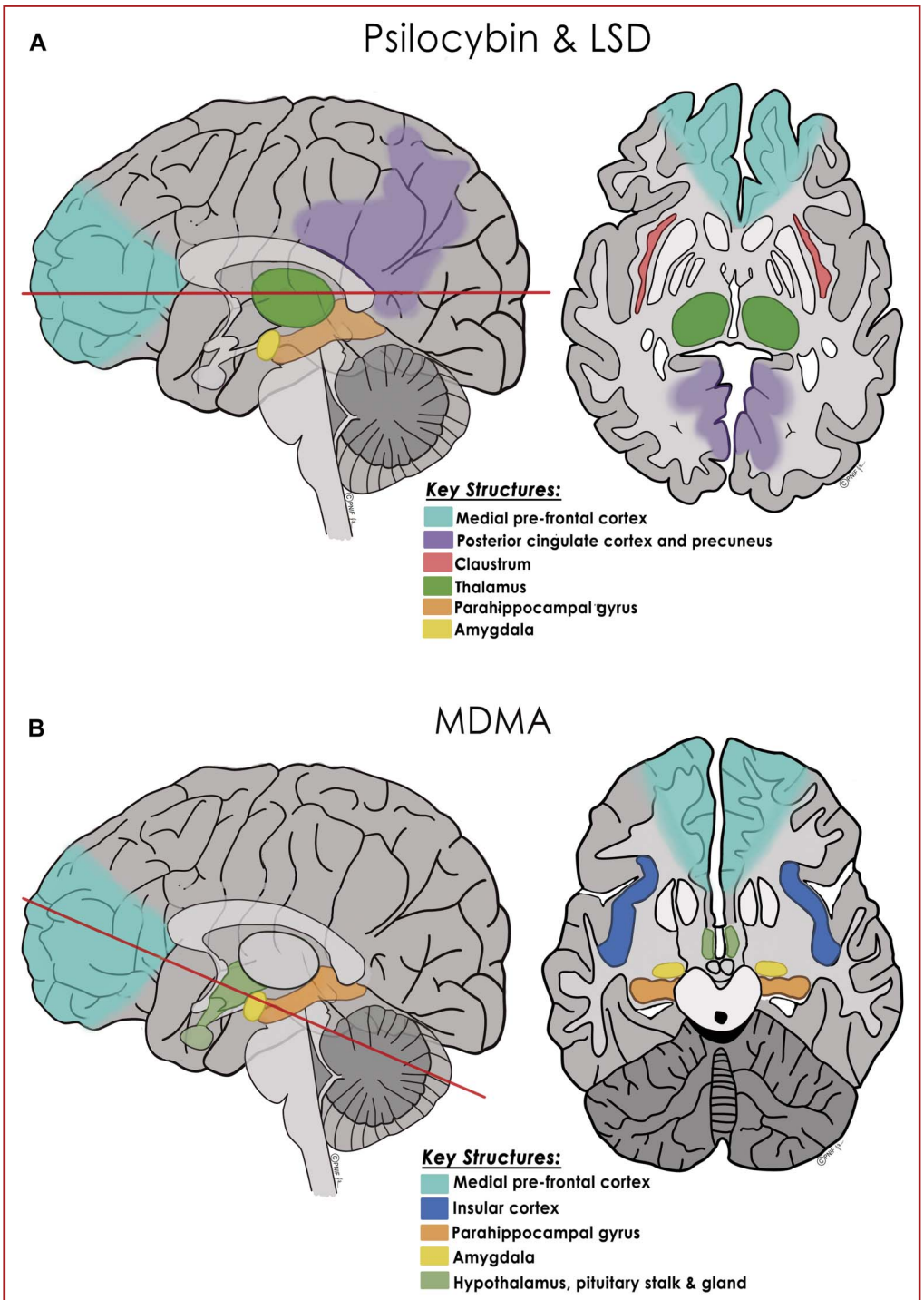

FIGURE 4. *Proposed key neural structures and mechanism of action of the classic psychedelics and MDMA.* **A**, *Psilocybin and LSD: Based on functional neuroimaging studies, sagittal and axial drawings show major brain regions altered by psilocybin and LSD (predominantly 5-HT$_{2A}$ receptor agonists): pyramidal neurons in the medial PFC, the DMN (including the posterior cingulate cortex and precuneus), and other networks such as the salience network, the thalamus, claustrum, parahippocampal gyri, and amygdala (red line in sagittal image denotes axial cut level).*[12,16,59-61,64] *Three functional models have been proposed for how the serotonergic psychedelics alter these cortical and subcortical structures and their regional connectivity. While they differ as*

FIGURE 4. *(continued) to the predominance of "top-down" or "bottom-up" loosening, all 3 models propose that the normally highly filtered flow of sensory information and access to autobiographical information is dampened or partially disrupted in the acute psychedelic state. This more connected state is proposed to lead to the commonly experienced auditory-visual synesthesias, visual hallucinations, alterations of space and time, alterations of one's sense of self, and in many patients, a mystical experience.*[59,60,63] *The CSTC model proposes that activation of medial prefrontal cortex 5-HT_{2A}R–containing neurons projecting to the striatum disrupts thalamocortical gating leading to reduced thalamic filtering of sensory information and increased signaling to the cerebral cortex, triggering synesthesias, cognitive, and emotional changes, and in some patients, ego dissolution.*[16,61,63,64] *The "relaxed beliefs under psychedelics" model proposes that psilocybin and LSD increase information flow from the hippocampus and parahippocampal gyrus to higher cortical areas, including the DMN, which relax high-level prior beliefs of one's sense of self, ego, and social identity.*[60] *This temporary disruption of the normal "top-down" constraint imposed over neural networks and sensory processing, along with favorable changes in amygdala responsiveness, is believed to halt or dampen ruminative thoughts and potentiate a more functionally connected and flexible brain.*[5,65] *The cortico-claustro-cortical model, focuses on the claustrum, situated between the insula and the putamen with a high density of 5-HT_{2A} receptors and considered critical in maintaining cortical networks including the DMN and frontoparietal network.*[59] *Based on fMRI data, psilocybin acutely decreases claustrum connectivity to auditory and other cortical areas with resultant alterations in perception and attention; this decreased cognitive control correlates with measures of a "mystical experience."*[12,59] **B**, *MDMA: Based on neuroimaging studies, sagittal and axial drawings show major brain regions and neurohormonal circuits altered by MDMA including connections between the medial PFC, the amygdala, parahippocampal gyri, and insula, as well as the hypothalamic-pituitary axis.*[34] *(Red line in sagittal image denotes axial cut level.) While MDMA does not seem to cause as much increased connectivity between neural networks as do psilocybin and LSD, MDMA-induced release of oxytocin (facilitated by serotonin efflux) affects connectivity between the medial PFC and amygdala, dampening amygdalar activation which may contribute to prosocial effects and memory reconsolidation. MDMA-induced cortisol release may also affect the amygdala and hippocampus, allowing extinction learning by facilitating emotional engagement despite revisiting fear and anxiety related to a traumatic event.*[34] *CSTC, cortico-striatial-thalamo-cortical; DMN, default mode network; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine.*

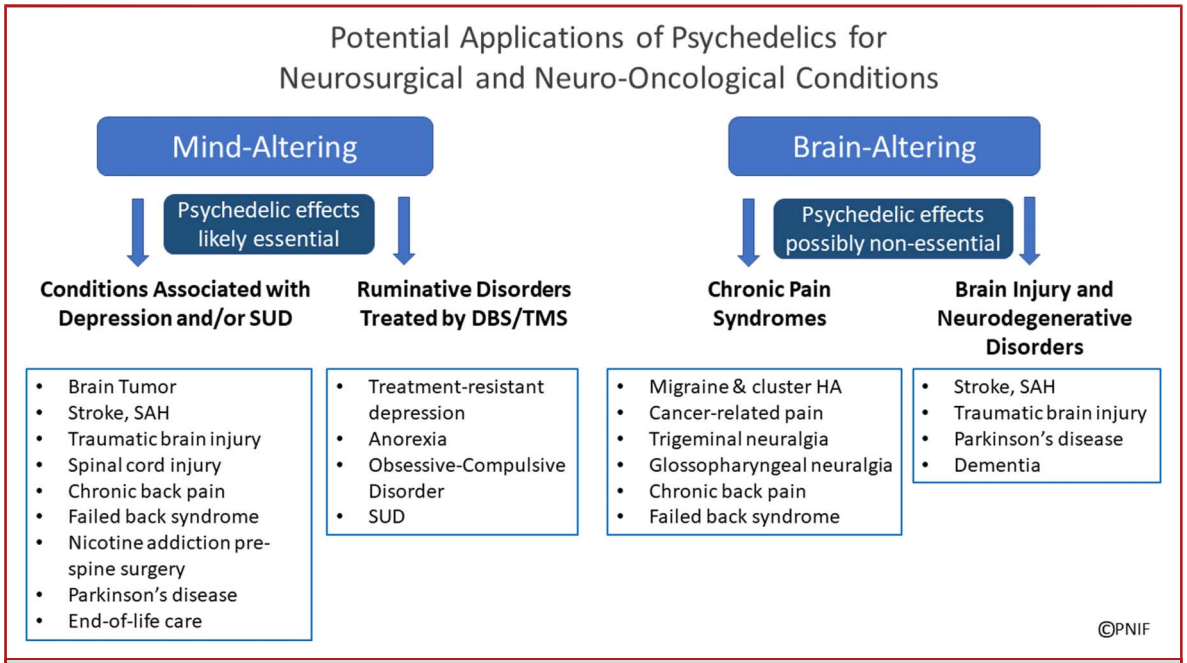

FIGURE 5. *Neurosurgery and neuro-oncology patient groups potentially affected by psychedelic-based treatments: Depicted are patient populations who may benefit from psychedelic-assisted therapy ("mind-altering" treatments) for depression, anxiety, and/or addiction (SUD), as well as those in clinical trials with DBS or TMS for ruminative disorders. Patients who might benefit from the neuroplastic potential of psychedelics (possibly without psychedelic effects at lower doses) are depicted as "brain-altering," including patients with chronic pain syndromes and those with brain injury (stoke, SAH, TBI) and neurodegenerative disorders. The potential overlap and synergy of these "mind-altering" and "brain-altering" psychedelic-based approaches warrant further investigation. DBS, deep brain stimulation; HA, headache; SAH, subarachnoid hemorrhage; SUD, substance use disorders; TBI, traumatic brain injury; TMS, transcranial magnetic stimulation.*

TABLE 2. Prevalence Rates of Depression, Anxiety, and SUD in Select Neurosurgical Diagnoses

Diagnosis	Depression (range)	Anxiety (range)	SUD[a] (range)
Brain tumor	3%-41%	5%-48%	NA
Stroke	20%-60%	8%-29%	8%-56%
Aneurysmal subarachnoid hemorrhage	0%-62%	40%-59%	19%-33%
Traumatic brain injury	17%-61%	18%-60%	5%-28%
Spinal cord injury	19%-26%	15%-32%	17%-68%
Chronic lower back pain/failed back syndrome	20%-64%	15%-28%	12%-36%
Trigeminal neuralgia/other pain syndromes	15%-65%	19%-50%	8%-12%
Parkinson disease	2%-57%	25%-52%	NA

NA, not available; SUD, substance use disorders.
[a]SUD includes for alcohol, opioids, and/or nicotine.
Refer to references:[76-104].

Regarding patients with brain tumor, despite having high rates of anxiety and depression, all PAT clinical trials have excluded such patients given concern that psychedelics may decrease seizure threshold.[78,103,104] However, there are no reports of seizures in recent clinical trials.[7-9,11] Notably, tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors all lower seizure threshold and have other side effects including cognitive impairment, sleep disturbances, and sexual dysfunction.[105,106] Interestingly, fMRI data show psilocybin induces decoupling of the medial temporal lobe to higher cortical areas and reduces interhemispheric communication, which may lower seizure risk.[13] Given the safety and efficacy thus far for psilocybin-assisted therapy, it is possible that many patients with brain tumor with depression, existential distress, fear of dying, and/or suicidal ideation could benefit.[9,11,68,78,107] Particularly in patients with malignant gliomas or metastatic brain tumors with a curtailed life expectancy, the relative immediacy of psilocybin on mood may be the greatest argument for its use. However, neural network integrity or lack thereof related to brain tumor location, surgical approach, and adjuvant therapies, may in part determine PAT efficacy and safety.[108,109]

Use of PAT for neurosurgical patients with SUD should also be considered.[46,79,110,111] For example, in spine surgery candidates, given that smoking is associated with lower fusion rates, and psilocybin-assisted therapy has shown promise in early trials for nicotine and opioid addiction, PAT could be considered preoperatively to improve fusion rates and to reduce opioid dependence postsurgery which may occur in up to 1/3 of such patients.[6,45,100,112,113]

RUMINATIVE DISORDERS, SUD, AND PTSD BEING TARGETED WITH NEUROMODULATION

DBS and TMS have both shown variable efficacy or been considered for treating OCD, anorexia, SUD, depression, and PTSD.[72-74,114-119] DBS which stereotactically targets focal nuclei and TMS which focally targets broader brain regions contrasts with the global approach of ingesting a 5-HT_{2A}-R agonist to more broadly alter neural networks. As psilocybin-assisted therapy has shown early efficacy for depression and addiction and is in Phase 2 trials for OCD and anorexia, the relative roles of PAT vs DBS and/or TMS warrant investigation. Such studies might show one approach outperforms another for certain subgroups in efficacy, safety, and cost, or PAT combined with neuromodulation may prove to be synergistic.[5,7,9,11,45,46,74]

CHRONIC PAIN

LSD was shown to be effective for patients with severe cancer-related pain in the 1960s. Recently, both psilocybin and LSD have shown efficacy for chronic pain, cluster headache, and phantom-limb pain in pilot trials, and a new trial is opening for chronic low back pain.[21,24,120-122] Classic psychedelics may not only favorably alter the perception and emotional overlay of pain but may potentiate downstream control through 5-HT_{2A} receptors involved in antinociceptive actions of the ventromedial medulla, thereby augmenting descending spinal cord inhibitory pathways.[120] Investigation of psychedelics for managing chronic spinal pain, failed back syndrome, cancer-related pain, trigeminal neuralgia, migraine, and cluster headache seems warranted.[21,81,120] A potential benefit of psychedelic-based therapies for chronic pain may be to help resolve coexisting opioid and/or alcohol addiction.[100,102,110,123]

BRAIN INJURY, STROKE, AND NEURODEGENERATIVE DISEASE

As psychedelics can potentiate neuroplasticity, their possible role in treating TBI, stroke, aneurysmal SAH, dementia, and Parkinson disease warrants exploration.[22,30,34,70,124,125] One approach may be to combine psychedelic therapies with TMS or stem cell therapy, both of which have shown limited success in clinical studies for these disorders.[75,126,127]

PSYCHEDELICS AND CONNECTOMICS

Another potential interface of psychedelics with neurosurgery and neuro-oncology is in gaining a clearer understanding of neural networks related to cognition and emotion in both healthy and neuropathological conditions. The Human Connectome Project has helped spawn a highly detailed yet evolving perspective on functional connectivity networks, which are foundational in models of depression, anxiety, cognitive deficits, and mechanisms of action for psychedelics.[12,59,60,109,128-130] Neurosurgery has been at the forefront of brain mapping and increasingly using more sophisticated Human Connectome Project–generated maps in preoperative planning and postoperative assessments for patients with intra-axial brain tumors.[108,109,131] The potential synergy of psychedelics as neuroplastogens, together with, neuromodulation techniques such as TMS and DBS, monitored by brain connectomics data, provides an opportunity to reimagine multimodal care for patients with brain tumors, brain injury, and neurodegenerative disorders.[132]

MULTIDISCIPLINARY PSYCHEDELIC RESEARCH

Leading psychedelic research centers have formed over the last 2 decades at Johns Hopkins University, New York University, Imperial College London, and the University of Zurich with many others recently created. In the past several years, for-profit startups have helped fuel psychedelic research. Until recently, there has been limited interest and support of psychedelic research at National Institutes of Health, but this is changing as evidenced by the 2022 National Institute on Drug Abuse and National Institute of Mental Health-sponsored "Workshop on Psychedelics as Therapeutics: Gaps, Challenges and Opportunities."[133] Going forward, broader multidisciplinary collaboration will help explore novel applications of psychedelic-based therapies. For example, our Pacific Neuroscience Institute *Treatment & Research In Psychedelics* program formed in 2019 is led by an addiction medicine specialist (K.H.) in collaboration with a psycho-oncologist (S.G.), neuro-oncologist (A.S.), and neurosurgeon (D.F.K.) and staffed by psychedelic guides (K.S.). We offer KAT and have completed enrollment for 2 psilocybin-assisted therapy clinical trials in collaboration with Usona Institute, including a pilot trial for AUD and a Phase 2 multicenter trial for major depression.

CONCLUSION

The fields of neurosurgery and neuro-oncology have contributed immensely to the betterment of patients with a wide spectrum of challenging neuropathology. The nascent field of psychedelic science offers potential new avenues for advancing and reshaping our approach to behavioral health care and to understanding and harnessing neuroplasticity. This review attempts to demonstrate convergent opportunities for psychedelic-based therapies within neurosurgery and neuro-oncology. While additional and larger clinical trials are clearly needed to better determine the potential risks and benefits of PAT across different patient populations, we encourage the neurosurgical and neuro-oncology communities to engage in this rapidly evolving field, thinking broadly and creatively as to how the safe and evidence-based use of psychedelics may affect patient care and research. Through such collaborative efforts in which psychedelics are viewed as both investigative and therapeutic molecules, we may enhance our patients' quality of life while gaining a better understanding of neural networks, neuroplasticity, the underpinnings of mental anguish, and the nature of mind itself.

Funding

This work has been in part supported by a gift from the Annenberg Foundation and support from Pacific Neuroscience Institute Foundation and Saint John's Health Center Foundation. Dr Kelly, Dr Heinzerling, and Dr Sergi receive clinical trial support from Usona Institute.

Disclosures

Dr Kelly has stock in MindMed, Numinus, and Noetic Fund. Dr Heinzerling is a consultant for MindMed. Dr Sergi is a consultant for Field Trip Health and has stock in Compass Pathways, Field Trip Health, and MindMed. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

We acknowledge Professor David E. Presti for his helpful critique and detailed suggestions on the manuscript. We also acknowledge collaborations from Carmen Kelly for creating Figure 3 and from Josh Emerson for creating Figure 4A and 4B.