Novel Pharmacologic and Other Somatic Treatment Approaches for Posttraumatic Stress Disorder in Adults: State of the Evidence

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Posttraumatic stress disorder (PTSD) is a highly prevalent psychiatric disorder that can become chronic and debilitating when left untreated. The most commonly recommended first-line treatments for PTSD among adults are individual trauma-focused psychotherapies. Other evidence-based treatments include specific antidepressant medications and non-trauma-focused psychotherapies. Despite the effectiveness of these available treatments, many patients' symptoms do not remit. This has led to the search for novel treatments for PTSD. In this review, the authors critically evaluate the data supporting several emerging pharmacological and other somatic interventions in the categories of medication-assisted psychotherapy, novel medication monotherapy strategies, and neuromodulation, selected because of the salience of their mechanisms of action to the pathophysiology of PTSD (e.g., MDMA-assisted psychotherapy, ketamine, cannabidiol, transcranial magnetic stimulation). The authors also evaluate the evidence for treatments that are the focus of increasing scientific or public interest (i.e., hyperbaric oxygen therapy, stellate ganglion block, neurofeedback). To date, the evidence supporting most novel pharmacological and somatic treatments for PTSD is preliminary and highly variable; however, the data for several specific treatments, such as transcranial magnetic stimulation, are encouraging.

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Posttraumatic stress disorder (PTSD) is a potentially disabling psychiatric disorder (1) with worldwide lifetime prevalence of 3.9% (2). PTSD is more common among individuals who experienced childhood adversities (3) and groups at high risk for trauma exposure such as active-duty military servicemembers and veterans (4). There is general agreement across clinical practice guidelines (CPGs) about which treatments are most effective for treating PTSD among adults. However, no treatment is effective for all patients, so the search for novel treatments for PTSD has continued. In this review, following a brief overview of current evidence-based treatments for adults with PTSD, we describe several novel pharmacological and somatic treatments currently in development for PTSD and provide a critical assessment of the empirical support for each. Finally, we make recommendations to guide clinical decision-making and future research.

Current CPGs for PTSD are aligned in providing the highest strength of recommendation for trauma-focused psychotherapies (TFPs; see Table 1) (5–7). Recommended TFPs include prolonged exposure (PE) (8), cognitive processing therapy (CPT) (8), and eye movement desensitization and reprocessing (EMDR) (9). There is less—but still substantial—agreement about the strength of recommendations for other psychotherapies, such as present-centered therapy (10).

Conversely, there is moderate variability in the strength of the pharmacotherapy recommendations. While all current CPGs identify the same medications as effective (i.e., sertraline, paroxetine, and venlafaxine [the U.S. Food and Drug Administration has only approved sertraline and paroxetine for PTSD]), recommendations range from low (from the International Society for Traumatic Stress Studies), to strong (from the United States Department of Veterans Affairs and Department of Defense [VA/DoD]) (5, 7). Although specific medications and TFPs have the same strength of evidence, TFPs are recommended before medications by several CPGs (see Table 1).

As with all psychiatric conditions, it is unlikely that any one intervention will adequately treat all patients with PTSD. Some patients decline first-line treatments or discontinue prematurely, and of patients who engage, a sizable minority do

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TABLE 1. Key recommendations of clinical practice guidelines for the treatment of PTSD[a]

	Clinical Practice Guideline				
Treatment	APA, 2017	VA/DoD, 2023	NICE, 2018	Phoenix, 2020	ISTSS, 2020
Psychotherapy (individual)					
Cognitive processing therapy	Strong	Strong	Strong	Strong	Strong
Prolonged exposure	Strong	Strong	Strong	Strong	Strong
Eye movement desensitization and reprocessing	Moderate	Strong	Strong (for non-combat-related PTSD)	Strong	Strong
Trauma-focused cognitive therapy (CT)	Moderate	Moderate (Ehlers CT for PTSD only)	Strong	Strong	Strong
Narrative exposure therapy	Moderate	Insufficient	Strong	Moderate	Moderate
Present-centered therapy	[b]	Moderate	[b]	Moderate	Moderate
Pharmacotherapy (monotherapy)					
Select SSRIs (sertraline, paroxetine, venlafaxine)	Moderate	Strong	Moderate	Moderate	Moderate
Fluoxetine	Moderate	Insufficient	Moderate	Moderate	Moderate
Benzodiazepines	[b]	Strong *against*	[b]	[b]	[b]
Cannabinoids	[b]	Strong *against*	[b]	[b]	[b]
Risperidone	Insufficient	Moderate *against*	Moderate[c]	[b]	[b]
Prioritization of first-line treatment					
Trauma-focused psychotherapy> pharmacotherapy	[b]	Strong	Strong	Moderate	[b]

[a] Adapted from Hamblen et al. (2019) (5). Key recommendations for individual psychotherapy are those with ratings of "strong" or "moderate" by two or more CPGs. Key recommendations for pharmacotherapy monotherapy are those with a rating of "strong" by at least one CPG or "moderate" by two or more CPGs.
[b] Not specified.
[c] As adjunctive to psychotherapy and when symptoms are disabling and non-responsive to other treatments.

not respond. Indeed, depending on the population, between one-third to two-thirds of patients do not reach remission after receiving recommended treatments (11). Unfortunately, moderators of PTSD treatment response are not well understood, with evidence of few possible psychosocial predictors of poorer response to psychotherapies, such as combat exposure, participation in atrocities, and poorer mental health (12), and only preliminary evidence of neurobiological predictors such as resting-state functional connectivity (13, 14). Currently available treatments are not effective for all patients, and additional options are needed for both treatment-naïve and treatment-resistant patients.

NOVEL APPROACHES TO TREATING PTSD

Treatment development for psychiatric disorders is typically based on theorized pathophysiology of the specific disorder. Historically, this strategy has conceptualized psychiatric illness in various ways. The first paradigm sees psychiatric illness as arising from dysfunctional thoughts and behaviors, which supports the development of psychotherapies, with evidence that TFPs are indeed effective via changes in posttraumatic cognitions and extinction learning (15). In the second paradigm, psychiatric illness is conceptualized as arising via disrupted neurochemical and hormonal signaling, which supports the testing of medications; in some patients with PTSD, these disruptions include dysfunction in the noradrenergic system and hypothalamic-pituitary-adrenal (HPA) axis (16, 17). A third paradigm conceptualizes psychiatric disorders as arising from dysfunction within circuits of brain regions that regulate mood, thoughts, and behavior, which, in PTSD, might include disruptions in neural circuits serving threat processing (amygdala, insula, and anterior cingulate cortex), fear learning (amygdala microcircuits), emotion regulation and executive functioning (medial, dorsolateral, and ventrolateral prefrontal cortices), and contextual processing (medial prefrontal cortex, thalamus, hippocampus) (18, 19). It is important to note that each of these paradigms and their distinct primary mechanisms of action and delivery methods result in altered neural circuitry, and interventions based within different conceptualizations could be combined for synergistic effects.

In what follows, we discuss areas of PTSD treatment development that are guided by these conceptualizations of the pathology of PTSD—specifically novel pharmacological augmentations of psychotherapy, medication monotherapies, and neuromodulation. We conclude with a brief review of other treatments proposed for PTSD that are not guided by these potential mechanisms but are the focus of increasing scientific or public interest. We do not review stand-alone psychotherapeutic approaches, as both new and established psychotherapies are addressed in depth by the aforementioned CPGs and other systematic reviews and meta-analyses (20); many psychotherapeutic approaches also have good evidence to support them at the population level and are reasonably widely implemented. It is beyond the scope of this review to consider treatments for the prevention of PTSD, either immediately following a trauma or in the setting of acute stress disorder; rather, this review is focused on treatment for PTSD. This review is intended to be brief, practical, and actionable, rather than exhaustive, with our goal being to identify promising new treatments and discourage use and research on others. Treatment selection

was guided by the authors' expert consensus, participation by some of the coauthors in the 2023 revision of the VA/DoD CPG (JLH, PPS, PEH), review of questions posed to the PTSD Consultation Program by providers in the field (PEH), and review of the PTSD Trials Standardized Data Repository (21) (JLH) and of clinicaltrials.gov (LMS, BK).

MEDICATION-ASSISTED PSYCHOTHERAPY

Effective psychotherapies for PTSD are largely predicated on psychological theories of PTSD. Central to these theories are learning principles like threat conditioning and extinction (targeted using exposure in the case of PE) and maladaptive beliefs (targeted using cognitive restructuring in CPT). Extinction, in particular, forms the basis of most animal studies of recovery from trauma and PTSD (18). The extinction learning that occurs via repeated exposure to feared stimuli in a safe context is argued to generate a new memory trace that competes with the previous fear memory in response to environmental cues. Memory reconsolidation has also been increasingly recognized as relevant to PTSD: each time a memory is recalled, it is rendered labile and then reconsolidated, meaning that the memory could be modified based on new experiences and then retained (22). Efforts to augment TFPs with medication are based on the premise that these psychological mechanisms of change—extinction learning and retention versus fear memory reconsolidation—can be potentiated with selective pharmacotherapies (23). Although not reviewed here, it is also worth noting that there are nonpharmacological interventions that have been tested as adjuvants to TFPs because of their effects on these mechanisms (e.g., aerobic exercise, which enhances extinction and has been shown to potentiate PE) (24).

MDMA-Assisted Psychotherapy

MDMA increases synaptic levels of serotonin, norepinephrine, and dopamine through the blockade of reuptake transporters and stimulation of presynaptic release (25). The best studied protocol for MDMA-assisted psychotherapy administers a dose of MDMA prior to two or three 8-hour-long sessions of nondirective psychotherapy (26, 27). MDMA-assisted psychotherapy sessions are preceded and followed by three 90-minute psychotherapy sessions without MDMA. Based on preliminary evidence of durable (12 months) benefit (28), the FDA designated this intervention as a "breakthrough therapy," allowing it to be evaluated with an accelerated FDA review process. In the first phase 3 study of MDMA-assisted psychotherapy (29), at the primary endpoint (8 weeks after the final of three experimental sessions), the MDMA group had greater reductions in PTSD symptom severity, higher response and remission rates, and a greater proportion of participants who no longer met criteria for a PTSD diagnosis compared with those who received placebo. The second phase 3 study similarly found improvements in PTSD symptom severity, as well as functional impairment, among a more diverse sample than in previous studies (30). To date, the mechanisms underlying MDMA-assisted psychotherapy are not firmly established, with evidence from the published randomized clinical trials (RCTs) suggesting potential roles of increased openness to experience (31). MDMA also facilitates extinction (32) and so is being examined as an enhancer of PE (NCT05746572**)** (33). The published findings are encouraging, but assessing the potential value of this intervention is challenging due to difficulties with blinding (and potentially biased results), poor characterization of adverse events in clinical trials to date that limits knowledge of potential risks (34), shortage of evidence regarding long-term safety and MDMA abuse potential, and the resource-intensive nature of this protocol that will likely serve as an impediment to implementation. This may be especially true in publicly funded healthcare systems, both inside and outside of the United States.

Ketamine-Assisted Exposure Therapy

Ketamine, an *N*-methyl-D-aspartate antagonist (35) that is effective for treatment-resistant depression (36), is being tested as an enhancer of psychotherapy for PTSD due to its potential to promote neurogenesis and neuroplasticity (37) and alter reconsolidation of traumatic memories (38). A recent pilot RCT of ketamine-assisted PE delivered in an intensive format found no difference between ketamine and midazolam in PTSD outcomes but did produce evidence that ketamine reduced amygdala and hippocampus reactivity to trauma memories (39). A follow-up study is ongoing (NCT05737693), as is a trial of outpatient PE augmented with intravenous ketamine or placebo (midazolam) at sessions one to three, followed by seven more PE sessions without augmentation (NCT04560660).

Psilocybin-Assisted Psychotherapy

Psilocybin is a psychedelic compound derived from several species of mushrooms, which has agonistic effects at the 5-HT2A receptor. Psilocybin impacts many processes relevant to PTSD recovery, including facilitation of extinction, promotion of neural plasticity, and reduced avoidance (40). Psilocybin-assisted psychotherapy has shown promising results in treatment-resistant depression, for which it has FDA "breakthrough therapy" status, but to date there are no published studies of psilocybin for PTSD (either as monotherapy or as adjunctive to psychotherapy). There are, however, several ongoing studies of psilocybin-assisted psychotherapy for PTSD (e.g., NCT05554094).

Cannabidiol (CBD)-Assisted Exposure Therapy

CBD is a component of the cannabis plant, which unlike tetrahydrocannabinol (THC), does not appear to produce hallucinogenic effects. CBD can facilitate the disruption of fear memory consolidation, promote fear extinction, and reduce post-traumatic avoidance behaviors in both humans and rodents (41). Again, these strong putative mechanisms and the strength of preclinical data make CBD-assisted exposure therapy worth further investigation. At least two

clinical trials of PE augmented with CBD are underway (NCT03518801, NCT05132699).

Other Medications

Several other medications with properties relevant to mechanisms of change in psychotherapy for PTSD have been proposed as therapy enhancers. For example, D-cycloserine (DCS) and hydrocortisone have strong putative mechanisms as therapy enhancers with evidence of relevant target engagement (42, 43). However, RCTs for these agents have been negative for their effect on PTSD symptoms (44–46), and although subsets of patients may respond preferentially (46, 47), it is our view that these treatments should not be prioritized for additional research. Others, such as intranasal oxytocin (48), propranolol (49), and yohimbine (50) have promising preliminary support as treatments when combined with psychotherapy for PTSD and require examination in larger trials. Although there are no ongoing trials of yohimbine, studies of oxytocin augmentation of psychotherapies for PTSD (e.g., NCT04228289, NCT04523922) and propranolol among youth and populations with co-occurring conditions are underway (e.g., NCT05692271, NCT04985344).

PHARMACOLOGICAL MONOTHERAPIES TARGETING NOVEL MECHANISMS OF ACTION

All antidepressant medications recommended for treatment of PTSD target serotoninergic and/or noradrenergic neurotransmission. Antidepressants are second-line treatments in several CPGs because their overall effect size appears to be smaller than that for TFPs (20). Efforts to develop novel medications for PTSD that exploit neurophysiological mechanisms beyond monoaminergic neurotransmission are underway (17). In general, the medications discussed in this section have been well-tolerated in clinical trials, and the risk of serious adverse events is generally low. However, these medications do differ in side effects and risks, and this should be considered when evaluating the risk-benefit ratio of their potential use.

Ketamine

Ketamine is being tested as a stand-alone treatment for PTSD because of its aforementioned effects on neurogenesis, neuroplasticity (37), and reconsolidation of traumatic memories (38). There is evidence supporting both a single intravenous infusion (0.5 mg/kg administered over 40 minutes, the same as used for treatment-resistant depression) (51) and repeated infusions (52) among civilians with PTSD. However, in a large study of repeated ketamine with the longest treatment duration to date, eight doses over 4 weeks did not outperform a saline placebo among veterans and servicemembers in terms of its effects of PTSD symptoms, despite benefit for depressive symptoms (53). The evidence base is therefore mixed and limited by small sample sizes in many studies, difficulty with blinding, and the relatively brief duration of symptom improvement, all of which contributed to its recent rating of "weak against" in the 2023 VA/DoD CPG (7). Additionally, it is not uncommon for treatments to perform less well in military samples than among civilians (54) and ketamine may still prove to be a useful strategy for reducing symptoms quickly, with clinical improvements that may persist long enough to stabilize a patient and support engagement in additional evidence-based care. And, as discussed above, ketamine remains under investigation as a psychotherapy enhancer. Ketamine infusions are generally well-tolerated by patients with PTSD, with few serious adverse events and greatest likelihood of mild and transient adverse events (e.g., blurred vision, dizziness, dissociation, agitation) occurring during the treatment infusion period during which patients are under observation (52, 53).

Cannabinoids

Whole plant marijuana and related cannabinoids have been tested for the treatment of PTSD. Although small pilot studies suggest benefit for treatment of specific PTSD symptoms (e.g., sleep disturbances and nightmares [55]), data on stand-alone cannabis for the overall treatment of PTSD are scarce (56), with some data suggesting chronic cannabis use is associated with impaired fear extinction (57). Currently, cannabinoids are not recommended for the treatment of any psychiatric disorder (58). The most recent RCT, with a two-stage design in which investigators compared three formulations of smoked cannabis, found no difference in efficacy for PTSD in any of the three active cannabis conditions compared with placebo (59). Further, analysis of national VA databases suggest that recreational cannabinoid use is associated with worsening PTSD outcomes for veterans in residential treatment (60, 61). Thus, known risks of cannabis currently outweigh the unknown benefits of cannabis in the treatment of PTSD (58), reflected in the recent "strong against" rating in the VA/DoD CPG (7). With the rapid shift in the legal landscape of cannabis regulation, larger controlled research trials investigating cannabis and other cannabinoids could be more feasible. At the same time, many U.S. states have gone beyond the evidence and certified PTSD as a condition approved for medical cannabis. This endorsement limits scientific equipoise and may make clinical trials harder to conduct, since patients with PTSD may not wish to participate in cannabis RCTs in which they could be randomized to placebo (58).

Other Potential Strategies

The evolving understanding of the pathophysiology of PTSD has led to the emergence of new targets for intervention that could introduce opportunities for precision medicine approaches to PTSD treatment (62).

Evidence of abnormalities in the availability of the cannabinoid receptor 1 (CB1), which is involved in consolidation and extinction of trauma memories, suggests that the endocannabinoid system offers opportunities for more targeted intervention beyond cannabis itself (41). For example, inhibition of fatty acid amide hydrolase (FAAH; a key

enzyme involved in endocannabinoid metabolism) in healthy adults enhanced recall of fear extinction memory and decreased autonomic stress reactivity (63).

Targeting the HPA axis is another potential strategy for treating PTSD. However, RCTs of two medications (corticotropin-releasing hormone receptor 1 receptor antagonist GSK561679 [64] and the glucocorticoid receptor antagonist mifepristone [65]) failed to find benefit.

Converging evidence suggests that antihypertensive medications targeting the renin-angiotensin system may have benefit in managing PTSD symptoms. This evidence includes retrospective data showing that individuals taking these medications have lower levels of PTSD severity, as well as preclinical data supporting a role of the renin-angiotensin system in stress-related pathology (66). However, a relatively large RCT of losartan, an angiotensin II receptor antagonist, did not find benefit for PTSD, though there may be the possibility that this or similar agents may still be beneficial in specific subgroups (67).

Alterations in the immune system/neuroinflammation (68) and glutamate signaling (69) have also been observed in PTSD. Development of therapeutic agents targeting these and other systems described here is highly preliminary at this time, but there is hope that these lines of research will identify effective treatment strategies. Fatty acid amide hydrolase (FAAH) inhibitors in particular are worth additional exploration given the strong preclinical support for endocannabinoids (70) and evidence that they target several crucial features of PTSD in humans (63).

MODIFYING DYSREGULATED NEURAL CIRCUITRY THROUGH NEUROMODULATION

Several neuromodulation approaches have emerged over the past few decades that are intended to specifically target dysfunctional neural circuits underlying psychiatric illnesses. Developing these neuromodulation strategies for the treatment of PTSD requires first identifying rational targets on the basis of the neural circuitry presumed to be disrupted in PTSD (i.e., prefrontal and limbic pathways that mediate fear learning, salience detection, executive functions, and contextual memory processing) (18, 71). Particular targets may be accessible via relatively noninvasive brain stimulation approaches, whereas others would require targeting via more invasive techniques (72). Further, as with medications, neuromodulation can be used as a stand-alone intervention or to enhance another treatment, such as a TFP.

Transcranial Magnetic Stimulation (TMS)

TMS induces electrical stimulation of the underlying cortex through a coil that produces a rapidly changing magnetic field. The magnetic field is not impeded by the scalp and skull, so relatively focal stimulation is possible (i.e., a 2–3 cm area of the cortex). No anesthesia is needed, and TMS is associated with no adverse cognitive effects (73), so it can be delivered safely and noninvasively in the outpatient treatment setting. TMS parameters can differ across several domains, including location of stimulation (e.g., left or right prefrontal cortex), stimulation frequency, number of pulses delivered per treatment session and number of treatment sessions.

TMS has been most frequently used for the treatment of depression. Given the role of the prefrontal cortices in learning and processing of emotional information and their disruptions in PTSD (19), TMS could also be a reasonable treatment approach for PTSD. A meta-analysis of six sham-controlled studies found that TMS led to a statistically significant, large improvement of PTSD symptoms (74). However, these studies were quite heterogenous in the TMS parameters used (e.g., high frequency vs. low frequency vs. theta burst; stimulating left vs. right prefrontal cortex), so it remains unclear how to best treat PTSD with TMS. A meta-analysis suggested that low frequency TMS applied to the right prefrontal cortex may be most effective for PTSD, in part due to its greater tolerability and better safety profile, but more research is clearly needed to establish which parameters are effective in treating PTSD (75).

Intermittent theta burst stimulation (iTBS) delivers a very high number of TMS pulses over a short period of time using a unique stimulation pattern thought to mimic the rhythm of theta-gamma coupling, which is critical to cognitive processes–most notably memory (76). As such, iTBS may have unique physiological and behavioral effects compared to standard TMS, although this has not been established (76, 77). iTBS has shown efficacy in depression similar to standard TMS (78). The only RCT of iTBS for PTSD was negative (79), but a recent effectiveness study among veterans with depression found that PTSD and depressive symptoms improved with both iTBS and standard TMS (80).

Transcranial Direct Current Stimulation (tDCS)

tDCS uses weak electrical current applied to the scalp; it does not lead to neuronal firing directly but might change cortical excitability (81). tDCS has been tested for safety and successfully applied in several psychiatric disorders, with evidence of modest benefit for depression and low likelihood of adverse events (e.g., skin burns) when conventional parameters and devices with standard safety features are used (81). The only study of tDCS for PTSD compared the effect of 10 sessions of 2mA tDCS versus sham stimulation over the bilateral dorsolateral prefrontal cortex (location selected because of its role in fear regulation, including inhibition of amygdala reactivity [19]) and found statistically significant improvement in self-reported PTSD severity (82).

Cranial Electrical Stimulation (CES)

CES applies low intensity alternating current to the scalp or earlobes and has been commercially available for nearly 50 years. Prior to 1979, when the FDA began regulating devices, several CES devices were marketed for treatment of anxiety, depression, and insomnia (83). Since then, several

newer versions of these devices have received FDA clearance as technically equivalent to the earlier versions, even without supporting clinical trial data that show efficacy. This treatment approach is relatively safe (81) and affordable, but there remains a shortage of evidence for meaningful benefit in treating anxiety and depression symptoms (84, 85). An open-label pilot study of 4 weeks of CES in PTSD patients was associated with improvements in PTSD, depression, and pain severity with a smaller effect on insomnia (86). To date, there have been no controlled clinical trials testing CES devices for PTSD.

Deep Brain Stimulation (DBS)

DBS is an invasive neuromodulation approach approved by the FDA for refractory Parkinson's disease, essential tremor, and epilepsy as well as dystonia and obsessive-compulsive disorder under humanitarian device exemptions. DBS is conducted via surgically implanted intracranial electrodes that modulate neuronal activity in specific brain regions, powered by subcutaneously implanted programmable pulse generators in the patient's chest. Studies suggest DBS works by altering neural activity both at the site of stimulation and in distal distributed networks (87). While evidence suggests that DBS is generally safe, the surgical procedure itself is expensive and can lead to adverse medical events; other types of serious adverse events (neurologic, psychiatric, and device-related) have also been observed in populations among whom there have been RCTs (i.e., those with refractory OCD) (88). Published case studies of DBS to treat PTSD with stimulation delivered to the medial prefrontal cortex (which mediates emotion regulation and executive function [19]) and uncinate fasciculus (89) or subgenual cingulum and uncinate fasciculus (90) suggest benefit from these approaches with risks similar to those observed in other populations, which could lead to them being appropriate for patients with highly treatment-resistant PTSD. The medial prefrontal cortex and uncinate fasciculus are targeted because they are very similar to the subcallosal cingulate DBS target that has shown preliminary efficacy in depression (91) and in preclinical models of PTSD (92). Similarly, the subgenual cingulum is homologous to the prefrontal structures that mediate extinction behavior in preclinical studies (92).

Vagus Nerve Stimulation (VNS)

VNS involves surgical placement of electrodes around the left vagus nerve in the neck, which are then connected to a pulse generator typically implanted subcutaneously in the chest wall. VNS is approved by the FDA for the treatment of epilepsy and treatment-resistant depression. To date, there are no data evaluating VNS as a treatment for PTSD, so safety and efficacy have not been established in this population, but preclinical work suggests potential for this intervention (93, 94). Noninvasive forms of VNS (transcutaneous VNS [tVNS]) have lower risk profiles (due to no need for surgery) and may warrant further study (95, 96).

Neuromodulation-Assisted Psychotherapy

Neuromodulation could also serve to enhance the effects of other treatments, namely psychotherapy. In one study, TMS delivered prior to sessions of CPT significantly enhanced the efficacy of this psychotherapy in combat veterans with PTSD (97). Another small trial found that TMS with an H coil (the geometry of which was designed to stimulate both superficial PFC and deeper subregions) after a brief trauma exposure at each treatment session was more effective than sham stimulation or active TMS paired with a control exposure condition (98). A subsequent larger trial with a similar design found that active stimulation in combination with PTSD symptom provocation was less effective than sham stimulation with the same symptom provocation (99). It should be emphasized that this study delivered TMS *after* the brief exposure to a personalized trauma narrative, which may have interfered with fear extinction (100). There is also preliminary evidence supporting tDCS combined with exposure therapy for PTSD (101).

OTHER PROPOSED TREATMENTS

Several treatments have been proposed for PTSD that do not easily fit the previous categories. The efficacy of these treatments might be based on anecdotal reports of efficacy that generate significant public interest in the absence of rigorous clinical trial data. For others, more rigorous clinical trial support exists. In this section, we review three treatments that have generated positive preliminary signals in clinical studies. Due to their regulatory approvals for other conditions, these treatments are available in clinical settings and providers can use them off label. However, we emphasize that none of the treatments in this section are currently recommended for the treatment of PTSD (5).

Neurofeedback

Neurofeedback is a specific type of biofeedback in which individuals learn to control their physiological functions by monitoring and responding to a real-time report of a specific physiologic signal. In electroencephalogram (EEG)-driven neurofeedback, neural activity is recorded from scalp electrodes, and feedback of the recorded brainwaves is provided in real-time to the participant in a readily understood format (e.g., visual or auditory presentation). Participants then learn to regulate brainwave patterns associated with certain targeted cognitive processes or symptoms through positive or negative feedback (102). In functional magnetic resonance imaging (MRI)-driven neurofeedback, the participant is provided with visual feedback on a monitor, while in the MRI scanner, about the level of neural activation in the target brain region or network, and they then use different cognitive strategies to increase or decrease that target activity (103). Extant studies suggest that self-regulation of specific brain signatures seems viable and can produce reduction in symptoms (102, 104, 105). Clinical improvement after neurofeedback was associated with normalized brain connectivity (104) and

wave patterns in several canonical PTSD regions (105), but also normalization of activation in other brain regions that correlated with symptom reduction. In a small RCT of stand-alone fMRI-driven amygdala neurofeedback, three sessions of neurofeedback after trauma cueing led to no treatment-related adverse events and outperformed sham for improving amygdala control, but not PTSD symptom severity—likely because of the large improvements observed in the control group and small sample size (106). In that study, the active group demonstrated greater ability to decrease amygdala activity than the sham group—but again PTSD symptoms did not statistically differ (106). Two recent studies of EEG-based neurofeedback (one open trial [107], one RCT [108]) delivered adjunctive to treatment-as-usual found evidence of improved PTSD symptom severity. The safety profile and preliminary data supporting neurofeedback techniques suggests that they may be worth replication in larger trials.

Stellate Ganglion Block (SGB)

SGB involves one or more injections of a local anesthetic (e.g., ropivacaine) into a nerve bundle called the stellate ganglion, located between the C6 and C7 vertebrae. The stellate ganglion is a major node within the sympathetic nervous system and contains both afferent and efferent nerve fibers. SGB has been used safely and successfully for a variety of conditions, such as complex regional pain syndrome (109) and peri-menopausal hot flashes (110). Risks are largely limited to bruising or pain at the injection site. The mechanism by which temporary interruption of the cervical sympathetic nerve bundle could improve PTSD is unclear, but several case series (111) and open-label studies suggested benefit and prompted larger-scale investigation of SGB, administered as a pair of two injections over 2 weeks (112). Evidence from controlled studies is mixed; one RCT of a single SGB versus a sham procedure did not find a significant differential effect for SGB versus sham on PTSD severity (113). However, a subsequent, larger sham-controlled RCT of two injections did show significant benefit for PTSD symptoms at the primary (8-week) endpoint, with no serious adverse events (114). Limitations of both RCTs included a relatively short follow-up period of 4–6 weeks and use of unblinded treatment administrators. In two small, unblinded studies, investigators augmented exposure therapy for PTSD with SGB, finding large improvements in PTSD (115, 116). Overall, SGB has mixed support to date, but the suggestion of a signal for efficacy warrants additional study. A large, multisite RCT in veterans (NCT05169190) should provide more definitive evidence of the utility of SGB for PTSD.

Hyperbaric Oxygen Therapy (HBOT)

HBOT is designed to increase the supply of oxygen to blood and tissue. Following certain injuries, there is an increased demand for oxygen to supply the cellular machinery necessary for the repair processes. The FDA has cleared HBOT for treating several medical conditions including decompression sickness, carbon monoxide poisoning, and burns. The most common risks are minor ear problems, such as pain and other conditions caused by significant shifts in water or air pressure (e.g., inner ear barotrauma) (117). Although case-control studies have shown benefits of HBOT among patients with PTSD and traumatic brain injury (118), findings have not been reliably replicated in RCTs (117). The most recent RCT, which compared 40 HBOT versus sham chamber sessions over 12 weeks, showed acute benefits for post-concussive and PTSD symptoms after 13 weeks of treatment, but not at 6 and 12 months after treatment (119). The shortage of positive long-term data, coupled with the challenges of sham design and cost of HBOT, suggest that it is unlikely that additional research would show that this is a valuable approach to add to the array of treatments for PTSD.

CONCLUSIONS AND RECOMMENDATIONS

Moving forward, to advance the field meaningfully for both treatment-naïve and treatment-resistant patients, we recommend a three-pronged approach to treatment development: 1) improve existing evidence-based treatments (e.g., through pharmacological or neuromodulatory augmentation); 2) develop novel treatments based on unique or alternative neurobiological mechanisms; and 3) identify biological and psychological markers that predict which patients are more likely to respond to which treatments.

We have described several efforts in these domains, summarized in Table 2. Among the medication-assisted psychotherapy protocols, MDMA-assisted psychotherapy has garnered the most enthusiasm and has the largest evidence base, which may lead to its having FDA approval in the near future. The search for novel medications to treat PTSD is being guided by neurochemical mechanisms beyond monoaminergic neurotransmission. Ketamine and cannabinoids both have strong putative mechanisms and some supporting data, although other strategies await further exploration.

Of the device-based neurostimulation treatments being developed for PTSD, TMS is the only such treatment that has surpassed the experimental stage and been investigated in controlled clinical trials, both as a stand-alone treatment and as an adjunctive treatment for potentially enhancing TFP. At this point it is also highly scalable from a resource allocation perspective, since the devices historically used for depression treatment are also available for treating PTSD, and TMS delivery can be monitored by paraprofessionals. However, efficacy of protocols used in these trials was not confirmed or robust, suggesting more work is needed to identify optimal stimulation parameters for treating PTSD.

Additional novel treatments, such as SGB and neurofeedback, currently lack sufficient efficacy and safety data from rigorous clinical trials to comprise a standard of care for PTSD. Additional investigation is needed to determine whether or how SGB and neurofeedback will eventually be used in standard clinical practice. Additional research on HBOT, in contrast, is unlikely to lead to it being recommended for PTSD.

TABLE 2. Critical summary of novel approaches for treating PTSD

Treatment	Critiques and considerations	CPG recommendations to date
Most promise and most scalable		
Transcranial magnetic stimulation	• Optimal parameters not yet known • Could be used alone or combined with psychotherapy • Already used for depression in clinical practice and among most highly scalable of novel treatments for PTSD	2023 VA/DoD CPG: Insufficient evidence 2020 ISTSS CPG: Emerging recommendation 2018 NICE CPG: Insufficient evidence
Potential promise but challenges		
MDMA-assisted psychotherapy	• Highly resource intensive • Uncertain risk-benefit ratio	2023 VA/DoD CPG: Insufficient evidence
Ketamine (monotherapy)	• Mixed database • Known risks • Could be used to stabilize patients quickly before engagement in recommended treatments	2023 VA/DoD CPG: Weak against 2020 ISTSS CPG: Insufficient recommendation
Stellate ganglion block	• Mixed database • Unknown duration of benefit • Resource intensive	2023 VA/DoD CPG: Insufficient evidence
Neurofeedback	• Mixed database • Variation in experimental protocols • EEG-guided more scalable than fMRI-guided	2023 VA/DoD CPG: Insufficient evidence 2020 ISTSS CPG: Emerging recommendation 2018 NICE CPG: Insufficient recommendation
Insufficient information, future research recommended		
Cannabidiol-assisted exposure therapy	• Strong mechanistic evidence in rodents and humans • Two ongoing trials of PE augmented with cannabidiol	None
Ketamine-assisted exposure therapy	• Strong mechanistic evidence in rodents and humans • Two ongoing trials of PE augmented with ketamine	None
Psilocybin-assisted psychotherapy	• Strong mechanistic evidence in rodents and humans • Several ongoing trials	2023 VA/DoD CPG: Insufficient evidence (for psilocybin monotherapy)
Cannabinoid monotherapy	• Negative RCT of smoked cannabis • May effectively treat specific PTSD symptoms • VA/DoD CPG for PTSD recommends against use in practice because known risks outweigh unknown benefits	2023 VA/DoD CPG: Strong against
FAAH inhibitors	• Strong preclinical and mechanistic evidence in humans • No RCTs to date	None
Drugs that target HPA axis dysregulation	• Strong mechanistic evidence • Current medications (e.g., GSK561679, mifepristone) not effective	None
Antihypertensive medications	• Failed RCT of losartan • Possible benefit in subgroups	None
Transcranial direct current stimulation	• Safe with modest benefit for depression • One positive RCT in PTSD • Pilot data supporting combination with exposure therapy	2023 VA/DoD CPG: Insufficient evidence

continued

TABLE 2, *continued*

Treatment	Critiques and considerations	CPG recommendations to date
Cranial electrical stimulation	• Relatively safe and affordable • Lack of evidence for benefit for anxiety and depression • No RCTs	2023 VA/DoD CPG: Insufficient evidence
Deep brain stimulation	• Highly invasive • Successful preclinical and case studies in PTSD; no RCTs • May be appropriate for treatment-resistant PTSD	None
Vagus nerve stimulation	• FDA-approved for treatment-resistant depression • Data in PTSD limited to preclinical studies	2023 VA/DoD CPG: Suggest against
Unlikely to enter clinical practice, future research not recommended		
Hyperbaric oxygen therapy	• Mixed database • Benefits in largest RCT not sustained • Difficulty with blinding • High cost	2023 VA/DoD CPG: Insufficient evidence
D-cycloserine-assisted exposure therapy	• Evidence of target engagement • Mostly null RCTs	None
Hydrocortisone-assisted exposure therapy	• Evidence of target engagement • Two null RCTs	None

Most of the research reviewed here took place in high-income countries such as the United States and United Kingdom. Several of these protocols (such as MDMA-assisted psychotherapy and ketamine) require heavy allocation of resources, including licensed provider and nursing staff time, and controlled conditions in medical settings. Trauma is omnipresent, and PTSD is common, in many lower-income countries that do not have the adequate resources for implementation of many of the novel interventions discussed here. There remains a distinct need for development and implementation of scalable interventions for PTSD and increased opportunities for individuals from economically disadvantaged settings to participate in trials. Transdiagnostic psychosocial interventions may be the most practical for low-income countries, as they do not require the same level of mental health infrastructure and training as do TFPs, and studies support their use for PTSD and other psychiatric disorders in under-resourced settings (120, 121). That being said, certain interventions, such as TMS and EEG-guided neurofeedback, operate on a model that may be quite scalable in low-income countries; although these device-based treatments require financial investment up front, the maintenance costs are relatively minimal compared with those of ongoing psychological and pharmacological treatments.

For clinicians treating PTSD, TFPs are clearly the first-line approach. When TFPs are not available or preferred, clinicians should recommend select antidepressants and some non-trauma-focused psychotherapies. CPGs can also include information intended to aide providers and patients in shared decision-making and treatment planning, such as the treatment algorithms (7) and implementation considerations (6). Lang and colleagues (122) present guidance for clinicians on implementing the 2023 VA/DoD CPG, including strategies for treatment planning in settings in which recommended treatments are not feasible and with individuals who do not wish to engage in TFPs.

Beyond these guidelines, caution is warranted, as nearly all other treatments are under active investigation, with no research evidence to inform which treatment may be most effective for whom and in what sequence. Evidence from rigorous RCTs is needed before adoption of new treatments in routine clinical practice, particularly when the risk-benefit ratio is high. As with other medical conditions, patients with PTSD should be educated about the limits of the available evidence for both conventional and novel interventions and informed about which treatments are most likely to address their PTSD symptoms. Given finite resources in the healthcare system, it is practical to direct patients toward the most cost-effective and evidence-based treatments first. When patients' symptoms have not responded to evidence-based treatments, providers should explore which experimental treatment options are available locally, encourage patients to consider participating in clinical trials, or both. If and when novel medications are available as both monotherapies and psychotherapy adjuvants (e.g., ketamine, cannabidiol, TMS), and until there are head-to-head trials that inform which treatment is best for whom and whether combination treatments are more effective, providers and patients will need to consider the combination of risk profiles, patient burden, and potential duration of benefits when deciding which treatment to pursue.

A pronounced gap hindering the evaluation of relative efficacy of new or established PTSD treatments is the lack of consensus on what defines a meaningful treatment response and nonresponse (123). Further, the development of evidence-based treatment algorithms is needed and would

be supported by more head-to-head comparisons of currently available treatments (124), doubly-randomized preference trials (125), and tests of treatment switching for patients who do not respond to one type of treatment (126, 127). Finally, it will be critical to continue identifying biological, psychological, and other markers that can predict which treatment a patient's symptoms might, or might not, respond to. Ideally, decision-making about PTSD treatment will be informed by the emerging literature on personalized medicine, such as biomarkers of response and nonresponse and pharmacogenetics.

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Examination Questions for "Novel Pharmacologic and Other Somatic Treatment Approaches for Posttraumatic Stress Disorder in Adults: State of the Evidence"

1. **Clinical practice guidelines for PTSD recommend both psychological and pharmacological treatments; which of the following represent the specific class of treatment with the highest strength of recommendation?**
   A. Present-centered therapy
   B. Trauma-focused psychotherapy
   C. Interpersonal therapy
   D. Select antidepressants
2. **Which of the following represents the novel treatment with the most promising preliminary evidence combined with the greatest scalability?**
   A. Transcranial magnetic stimulation
   B. FAAH inhibitors
   C. MDMA-assisted psychotherapy
   D. Neurofeedback
3. **The authors recommend the following approach to PTSD treatment development:**
   A. Improve existing evidence-based treatments (e.g., through pharmacological or neuromodulatory augmentation).
   B. Develop novel treatments based on unique or alternative neurobiological mechanisms.
   C. Identify biological and psychological markers that predict which patients are more likely to respond to which treatments.
   D. All of the above