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MILITARY MENTAL HEALTH (CH WARNER, SECTION EDITOR)

The Walking Wounded: Emerging Treatments for PTSD

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Abstract

Purpose of Review We review the published literature over the last 24 months in the treatment of PTSD for our military men and women. We examined the updated clinical practice guidelines published in June 2017 by the Veteran's administration and Department of Defense and contrasted the guidelines with the most recent literature. We also discuss new directions in PTSD research.

Recent Findings Psychotherapy remains one of the most effective treatments for PTSD; unfortunately, few participants remain in treatment to completion. Many of the emerging therapies target NMDA receptor antagonists, cannabinoid receptor modulators, glucocorticoid receptor agonists, non-SSRI antidepressants, and opioid receptor agonists. The newer therapies fall into the drug classes of anti-hypertensives, glutamate modulators, oxytocin, and medication targeting insomnia/hyperarousal.

Summary PTSD symptoms are often chronic in our veteran population. While current treatments are helpful, there are often significant residual symptoms. We reviewed the most recent improvements in treatment and discuss therapies that are in the research phase.

Keywords Posttraumatic stress disorder · Psychotherapy · Emerging pharmacotherapy · Glutamate modulators · Neuroactive steroids · Somatic therapies

Between 45 and 60% of patients with PTSD experience ongoing significant functional impairment.

Many military members witness horrific events and experience lasting physical and emotional distress. These stressors can overwhelm even the most mature coping defenses. As such, our active duty military members and veterans suffer higher rates of posttraumatic stress disorder (PTSD) [1] than the general population. Chronic PTSD leaves our bravest warriors at a higher risk of suicide, mood, substance use disorders, as well as increased morbidity and mortality from general medical illnesses [2]. One study surveyed cohorts of deployed National Guard members and those in the US Army at 3 and 12 months post-deployment. That study showed a stable rate of PTSD or depression with serious functional impairment in the army cohort over several months and an increasing rate in the National Guard. Furthermore, they noted that about half of the soldiers meeting "strict definition" of PTSD or depression also had "alcohol misuse or aggressive behaviors," demonstrating significant comorbidities. The authors noted that the lack of decrease in symptoms between 3 and 12 months could inform post-deployment care [3].

Veteran affairs (VA) and Department of Defense (DoD) published an updated clinical practice guideline (CPG) for management of PTSD in June 2017, based on literature reviewed through March 2016 [4]. This guideline provides easily accessible, evidence-based information, and a framework for shared decision making with patients. The work group noted that despite the use of evidence-based psychotherapeutic and pharmacotherapeutic interventions, a significant portion of subjects with PTSD do not respond adequately to treatment.

We review the literature published since March 2016 and explore emerging treatments for PTSD. Information regarding clinical trials is referred to by using NCT number: ClinicalTrials.gov identifier [5]. We will correlate this with the VA-DoD PTSD CPG June 2017 to reinforce the

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currently available evidence-based treatments and gain an understanding of emerging treatment options. We also compared the VA-DOD PTSD CPG guidelines, which are the most current and thorough, to guidelines published by the American Psychological Association (APA) [6], British Association of Psychopharmacology [7], World Health Organization (WHO) [8], and Canadian Clinical Practice Guidelines [9]. The most recent guidelines published by the American Psychiatric Association were from 2009 and thus were not included.

Established Treatments for Military and Veteran PTSD

Psychotherapies

VA-DoD PTSD CPG June 2017 recommends the use of individual, manualized trauma-focused psychotherapies as first-line treatment. These therapies have demonstrated greater and more persistent efficacy than pharmacotherapeutic approaches. A meta-analysis by Kline et al. of randomized control trials (RCT) evaluating long-term efficacy of psychotherapy in PTSD supports this recommendation [10]. Among the trauma-focused psychotherapies, prolonged exposure, cognitive processing therapy (CPT), eye movement desensitization, and reprocessing have the strongest evidence. Additionally, the work group found sufficient evidence to recommend specific cognitive behavioral therapies for PTSD, including brief eclectic psychotherapy, narrative exposure therapy (NET), and written narrative exposure. In contrast, the APA strongly recommended the use of cognitive behavioral therapy, cognitive therapy, prolonged exposure therapy, and CPT but only suggested the use of EMDR and NET. The APA did suggest that with more evidence the recommendation regarding EMDR and NET could change to "strongly suggest." The other guidelines recommended either a trauma-based CBT approach or EMDR as first line treatment.

As many of us know, if veterans stay in treatment, these therapies work well. Unfortunately, only 30% of veterans remain in treatment after nine sessions [11]. This may reflect their lack of faith in the treatment or the psychic pain the treatment may cause initially. One study looked at engagement in veterans who chose pharmacotherapy, psychotherapy, or both (Haller et al. 2016). Less than one-third (23.7%) chose psychotherapy alone and the largest group (44%) chose a combination. Veterans who chose pharmacotherapy, with or without psychotherapy, had greater PTSD and/or depression symptom severity than those who chose psychotherapy alone. Those who had pharmacotherapy in the past or at the time of enrollment were also more likely to choose that, alone or in combination with psychotherapy. Reasons for veteran's choices were not given and may be worth examining in future studies. In the meantime, the differences noted between the groups delineated by the authors may help inform collaborative treatment planning.

In the absence of trauma-focused psychotherapy, either pharmacotherapy or non-trauma-focused psychotherapy such as stress inoculation training, present-centered therapy, and interpersonal psychotherapy can be used. The VA work group and the APA found weak evidence for non-trauma-focused psychotherapy.

Neurobiology of PTSD

Thomas and Stein in *Novel pharmacological treatment strategies for posttraumatic stress disorder* [12] and Kelmendi et al. in *PTSD: from neurobiology to pharmacological treatments* [13] summarize the neurobiology of PTSD and discuss emerging medication options.

The prefrontal cortex, hippocampus, and amygdala comprise the fear circuit. PTSD involves overgeneralization of the fear response by the amygdala. Impaired fear extinction by the repression of the inhibitory effects of the prefrontal cortex on the amygdala leads to persistent core symptoms of PTSD (Fig. 1). Starting with the activation of the hypothalamus-pituitary-adrenaline (HPA) axis in the face of a traumatic event, several agents including glucocorticoids, neuropeptide Y, monoamines, glutamate, GABA, endorphins, and endocannabinoids play a role in the acute stress response. Dysregulation of any of these factors can lead to higher predisposition to PTSD. A survey by the VA PTSD psychopharmacology work group identified five top targets for emerging PTSD treatment. They were NMDA receptor antagonists, cannabinoid receptor modulators, glucocorticoid receptor agonists, non-SSRI antidepressants, and opioid receptor agonists [14].

The VA PTSD psychopharmacology work group noted the dearth of effective pharmacological agents for PTSD, called for efforts to further understand the neurobiological mechanisms of PTSD, and invested in translational research to identify novel therapeutic options [14].

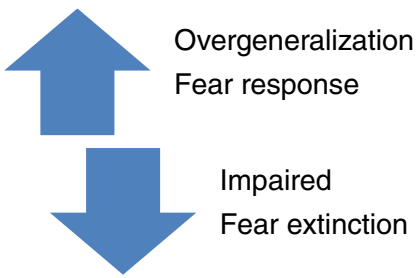

Fig. 1 Overgeneralization of the fear response and impaired fear extinction by the repression of the inhibitory effects of the prefrontal cortex on the amygdala

Established Pharmacotherapy

There are many different pharmacologic strategies for treating PTSD. However, only sertraline and paroxetine have been awarded approval by the Food and Drug Administration for the treatment of PTSD. They are the most extensively studied selective serotonin reuptake inhibitors (SSRIs) for this indication.

In terms of pharmacotherapy, VA-DoD CPG finds moderate quality of evidence for sertraline, paroxetine, fluoxetine, or venlafaxine. Research shows low evidence for nefazodone and very low evidence for imipramine and phenelzine. The potential for severe adverse events also limits the use of these agents.

In treatment refractory PTSD, clinicians may try various antidepressants, antipsychotics, mood stabilizers, and other psychotropic agents. VA-DoD PTSD CPG June 2017 recommends against using quetiapine, risperidone, olanzapine, and other atypical antipsychotics, citalopram, amitriptyline, lamotrigine, or topiramate as monotherapy due to the lack of strong evidence for their efficacy and/or known adverse effect/risk profiles. Insufficient evidence exists to recommend for or against monotherapy or augmentation therapy for the treatment of PTSD with eszopiclone, escitalopram, bupropion, desipramine, doxepin, D-serine, duloxetine, desvenlafaxine, fluvoxamine, levomilnacipran, mirtazapine, nortriptyline, trazodone, vilazodone, vortioxetine, buspirone, hydroxyzine, cyproheptadine, zaleplon, and zolpidem. This largely matches other guidelines, with the exception that the WHO recommends against SSRIs or TCAs as first line therapy for PTSD, in spite of limited psychotherapeutic resources in many parts of the world. This may be due to the better evidence behind therapy as a treatment for PTSD or concerns about risk versus benefits with medication especially surrounding TCAs. Also, the Canadian CPG still recommends augmenting with Zyprexa or Risperdal. However, this recommendation appears to be based on older data.

According to VA guidelines, there is insufficient evidence to recommend for or against the use of prazosin as mono- or augmentation therapy for nightmares. For global symptoms of PTSD, the guideline notes weak evidence against using prazosin. This somewhat controversial change from previous guidelines seemed to be weighted by the research published by Raskind et al. [15]. In a placebo RCT of "clinically stable" chronic PTSD patients, prazosin did not alleviate distressing dreams or improve sleep quality as measured by CAPS item B2—recurrent distressing dreams and Pittsburgh Sleep Quality Index (PSQI). The study seemed to be weighted towards a more stable population, as opposed to prior studies which had more clinically diverse populations. Furthermore, the population in the recent Raskind study had lower blood pressures than patients in previous studies. A secondary analysis of a previously randomized control trial suggested that higher standing blood pressure was a biomarker that helped identify combat veterans that would benefit from prazosin [16]. Many practitioners continue to utilize prazosin for nightmares, daytime flashbacks, and other PTSD symptoms despite CPG recommendations. This is likely due to concerns about the study by Raskind, anecdotal success, accessibility, and relatively low risk. An ongoing study, the prazosin and naltrexone (PaN) study for veterans with alcohol use disorders (AUD), NCT02322047 by Seattle Institute for Biomedical and Clinical Research/DoD-VA Puget Sound Health Care System, compares prazosin-placebo to prazosin-naltrexone using personalized script-induced alcohol craving in individuals with AUD, with and without comorbid PTSD.

Emerging Pharmacotherapy

Like prazosin, doxazosin blocks alpha-adrenergic receptors. A small open-label study [17] and a small placebo RCT [18] have shown beneficial effects of doxazosin ER (extended release) in treatment of PTSD, including reduction of nightmares. Its longer half-life offers a potential advantage over prazosin. The ER formulation allows for once-daily dosing. Clinical trials for doxazosin are ongoing. A clinical trial NCT02560805 by Emory University looks at the effect of losartan, another anti-hypertensive agent, on adrenaline levels in PTSD. It also explores the high adrenaline levels and higher risk of heart disease in subjects with PTSD.

Glutamate modulators (Table 1) have received a lot of interest over the last few years as a potential treatment option for several psychiatric disorders, including PTSD. Glutamate abnormalities and potential role of glutamate modulators are explored by Averill et al. in *Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies* [19•]. Exposure to trauma in vulnerable individuals leads to glutamate dysregulation, synaptic dysconnectivity, and dysregulation of fear and emotion circuits, leading to a higher risk of developing PTSD.

Riluzole, [20] a neuroprotective agent hypothesized to act by inhibiting glutamate and inactivating sodium channels, is currently approved by Food and Drug Administration (FDA) for treatment of amyotrophic lateral sclerosis (ALS). Several clinical trials are studying the possible benefits of Riluzole in mood and anxiety disorders,

Table 1 Glutamate modulators

Glutamate modulators
• Riluzole
• Ketamine
• D-Cycloserine
• *N*-acetylcysteine

Alzheimer's disease, and PTSD. Riluzole requires monitoring for elevated hepatic enzymes and neutropenia.

Krystal et al. [21•] in *Synaptic Loss and the Pathophysiology of PTSD: Implications for Ketamine as a Prototype Novel Therapeutic*, note that ketamine, an NMDA antagonist, may have quick benefits in PTSD, such as rapid antidepressant effects. These are attributed to ketamine's ability to reverse neuronal stress, which is mediated by several mechanisms. These include anti-inflammatory effects, increasing brain-derived neurotrophic factor (BDNF) levels, and re-establishment of better synaptic connectivity. Feder, Adriana, et al. [22], in a proof of concept trial, conducted a randomized, double-blinded, crossover study of single infusion of ketamine, with midazolam as an active placebo control in PTSD patients. They noted significant reduction in PTSD and comorbid depressive symptoms. Ketamine was associated with transient dissociative symptoms.

VA-DoD PTSD CPG June 2017 recommends against treating PTSD with ketamine. The work group noted limited information regarding the efficacy of ketamine in PTSD, concern for significant side effects, and abuse potential.

In addition to the concerns noted by the workgroup, several more have been noted as ketamine has been explored as an option for treatment-resistant depression. While ketamine offers a rapid onset of beneficial effects, the duration of these effects is relatively short, often lasting only a matter of days, and the long-term effects of repeated treatment remain unknown. Furthermore, ketamine has the potential to cause psychotic symptoms and requires careful dose titration. Nonetheless, in patients who do not respond to multiple treatment modalities, the benefits may outweigh the risks if emerging evidence supports it [23]. Ongoing trials will hopefully further our understanding of the long-term effects of ketamine on neuroplasticity, cognitive functioning, and the risk of dissociative symptoms and perceptual disturbances.

D-Cycloserine (DCS) is a partial NMDA agonist. VA-DoD PTSD CPG June 2017 notes that evidence is strong to recommend against use of DCS as monotherapy in PTSD due to limited evidence of efficacy. Ongoing studies are evaluating the use of the medication in combination with therapy. *Effect of D-cycloserine on a Short Imagery Rescripting Intervention for Subclinical PTSD*, NCT03216356 by Boston University Charles River Campus and James S McDonnell Foundation, a placebo-controlled RCT, is one such study.

Back et al. [24] explore the role of *N*-acetylcysteine (NAC) in PTSD and substance use disorders in veteran patient population. The FDA granted NAC the status of investigational new drug for this study. NAC modulates glutamate levels in nucleus accumbens. In this 8-week placebo-controlled study, participants received group cognitive behavioral therapy along with 2400-mg NAC or placebo. The NAC group was associated with significant improvements in PTSD, depression, and craving scores compared to placebo. The most common side effects were dry mouth and heartburn. The relative safety and the potential to treat multiple comorbid psychiatric disorders, including substance use, make this a particularly intriguing prospect.

Neuroactive steroids including glucocorticoids, 17β-estradiol, and GABAergic neuroactive steroids have been shown to regulate the fear pathway and facilitate fear extinction. They act by modulating neuronal signaling and by altering gene expression [25•]. However, the VA-DoD PTSD CPG June 2017 found insufficient evidence to recommend the combination of exposure therapy with hydrocortisone outside of the research setting. Ganaxolone (GNX) is a synthetic GABAergic neuroactive steroid. Rasmusson et al. [26] conducted a proof of concept study of GNX in PTSD. A 6-week RCT of GNX vs placebo was followed by an open-label phase in which all subjects were given GNX. Results showed that GNX did not differ from placebo on CAPS measurement. Identifying neural mechanisms of PTSD symptom reduction induced by combined estrogen and prolonged exposure therapy, NCT03371654 by University of Illinois at Chicago/NIMH, is an upcoming phase IV RCT studying the effects of placebo vs estradiol in women between the ages of 18 and 45 with PTSD receiving prolonged exposure therapy. Studies in healthy controls have suggested that elevated estrogen levels benefit extinction learning by promoting its consolidation and thus enhancing its recall when tested later for it. Studies in healthy controls have suggested that elevated estrogen levels benefit extinction learning by promoting its consolidation and thus enhancing its recall when tested later for it.

Kautz et al. [27•] in neuropeptide Y, resilience, and PTSD therapeutics note that neuropeptide Y (NPY) modulates stress and anxiety responses through its actions via NPY 1 and 2 receptors in several key areas regulating anxiety and fear including the prefrontal cortex, amygdala, hippocampus, anterior cingulate cortex, and hypothalamus. NPY 1 agonists and NPY2 antagonists have anxiolytic effects. NPY1 agonists act by inhibiting glutamatergic neurons. NPY2 antagonists act by blocking presynaptic auto receptors, inhibiting the negative feedback mechanism, which prevents decrease of NPY levels. Sayed et al. [28] studied NPY at various doses ranging from 1.6 to 9.6 mg in comparison with placebo in subjects with PTSD. Dosing was done after trauma-script provocation. Higher doses of NPY were correlated with better scores on Beck Anxiety Inventory, but not on State-Trait Anxiety Inventory.

Oxytocin plays a role in modulating stress-anxiety by acting on the oxytocin receptor (OTX) in the amygdala and the anterior cingulate cortex. In a placebo RCT, Sack et al. [29] showed that administration of intranasal oxytocin was correlated with reduced scores on the Responses to Script-Driven Imagery Scale (RSDI), especially avoidance scores, when provoked by trauma-script exposure. Nawijn et al. [30], in a placebo RCT using functional MRI, showed that intranasal

oxytocin promotes left anterior insula and right putamen responses which have been shown to be abnormal in subjects with PSTD and may facilitate sensitivity for social support and therapeutic alliance leading to better response and recovery from PTSD. A study by Koch et al. showed normalization of the amygdala functional connectivity after the patient received oxytocin [31]. Subjectively, the patient noted decreased anxiety and nervousness. Another recent study showed administration of oxytocin 40-IU BID within 12 days of trauma can reduce the severity of PTSD symptoms [32]. All these findings suggest that oxytocin may play a significant role in future treatments.

Mendoza et al. in [33] *Cotinine: A Therapy for Memory Extinction in Post-traumatic Stress Disorder* note that the cholinergic system, through its interactions with glutamate in the PFC and GABA in amygdala, can facilitate the fear extinction pathway and lead to improvement in PTSD symptoms. Cotinine, an agonist at presynaptic and postsynaptic α7nAChRs, can have several benefits. These include improved mood, learning, and memory.

BNC210, a compound being studied by Bionomics company [34], selectively targets the alpha 7 nicotinic acetylcholine receptors (α7 nAChR) and is a negative allosteric modulator. It has been shown to have anxiolytic properties. A phase II, placebo controlled RCT, NCT02933606, (RESTORE study) involving subjects with PTSD, is underway. In comparison to the benzodiazepine lorazepam, BNC210 has been shown to be well tolerated without adverse effects on sleep and cognition and to lack abuse potential.

Ben Sessa [35] in *MDMA and PTSD treatment. PTSD: From novel pathophysiology to innovative therapeutics* explores the controversies associated with 3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy and its reemergence in research setting. MDMA acts by promoting release of serotonin, dopamine, and noradrenaline. This leads to mood enhancing, anxiolytic effects. Effects at the alpha 2-adrenoceptor decrease hypervigilance and promote relaxation. While it has been shown to be safe in research setting, the potential for addiction exists. Insomnia and a risk of dystonia have also been noted.

Suvorexant is an orexin antagonist recently approved by the FDA for the treatment of insomnia. Orexin antagonists have been shown to dampen the arousal enhancing system in the brain during sleep, without hindering slow wave and REM activity. Animal studies have shown that they also facilitate extinction of conditioned fear. There are currently two phase IV studies studying effects of suvorexant in PTSD. One of these, suvorexant and trauma-related insomnia, NCT02704754, is testing the hypothesis that suvorexant will improve sleep. Suvorexant and sleep's benefits to therapeutic exposure for PTSD, NCT02849548, study the effects of suvorexant after a session of exposure-based intervention for PTSD on sleep, PTSD symptoms, and intersession habituation. Studies have shown that impaired sleep before psychotherapy causes less favorable outcomes. Sleep has been implicated in learning processes that are a key to adaptive processing of trauma memories such as extinction learning and generalization of extinction. This study attempts to show that improving sleep after a written narrative exposure will improve PTSD treatment outcomes.

Ramelteon, a melatonin receptor 1 and 2 agonist, is a generally well-tolerated, FDA-approved agent for treatment of insomnia. A phase IV placebo RCT, NCT03265951 will study the effects of ramelteon in veterans with PTSD with comorbid complex insomnia, which has been characterized as insomnia and comorbid obstructive sleep apnea (OSA). Continuous positive airway pressure (CPAP) non-adherence poses a common, significant barrier to treatment in veterans with comorbid PTSD and OSA.

Tonix Pharmaceuticals compound TNX-102 SL, low-dose cyclobenzaprine in sublingual tablets, received a Breakthrough Therapy designation by FDA for PTSD in December 2016. This was based on a completed phase II trial, NCT02277704, a 12-week RCT to evaluate the efficacy and safety of TNX-102 SL subjects with military-related PTSD and related conditions (AtEase STUDY) followed by a 12-week open-label extension study NCT02421679. Benefits of TNX-102 in PTSD are hypothesized to be related to *serotonin 2A receptor blockade* leading to increase in restorative slow wave sleep (SWS), *alpha-1 adrenergic receptor antagonism* resulting in reduction of trauma-related nightmares, and *antihistamine-1 receptor activity*, which leads to decrease in stress-induced increase in rapid eye movement (REM) sleep in preclinical studies [36] At present, TNX-102 is in a phase III 12 week RCT, to be followed by an open-label extension study NCT03110575.

Loflin et al. [37•] in *Cannabinoids as therapeutic for PTSD*, note that Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have potential to block reconsolidation of fear memories, reduce cue-elicited fear, and facilitate extinction of the memory. Cannabinoids have also been shown to improve mood and sleep. However, higher doses of THC can provoke hyperarousal, anxiety, and even paranoia. THC is associated with a "high" feeling and with tolerance; CBD lacks these characteristics. Upcoming studies will look at CBD individually and as a 1:1 combination of CBD:THC. Nabilone, a synthetic cannabinoid, acts like THC. New York State Psychiatric Institute and National Institute on Drug Abuse (NIDA) is conducting a study on its effects on cannabis users with PTSD. New York University School of Medicine/National Institutes of Health (NIH) NCT03248167, explores the hypothesis that oral cannabidiol (CBD) will reduce alcohol consumption in individuals with alcohol use disorder and comorbid PTSD. VA-DoD PTSD CPG June 2017 recommends against treating PTSD with cannabis or cannabis derivatives due to the lack of evidence for their efficacy, known adverse effects, and associated risks.

Somatic Treatments

VA-DoD PTSD CPG June 2017 found insufficient evidence to recommend for or against the repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), or stellate ganglion block (SGB). Other guidelines that were reviewed reached the same conclusion, but ongoing studies may prompt a change in the future.

VA evidence synthesis program [38] looked at the effectiveness of stellate ganglion block (SGB) in PTSD. SGB involves injecting a local anesthetic such as ropivacaine/bupivacaine. SGB might help with PTSD symptoms by inhibiting connections between peripheral sympathetic nerve system and regions of the cerebral cortex thought to be abnormally activated in PTSD. Participants have reported improvement within minutes to days of the procedure. Additionally, the dosing schedule may increase in compliance, as it does not require continuous daily or weekly administration. The document concluded that findings from the first RCT of SGB for PTSD were inconclusive.

Kozel et al. [39] completed a study of repetitive TMS (rTMS) with cognitive processing therapy (CPT), comparing it to sham TMS-CPT. rTMS administered to right dorsolateral prefrontal cortex (rDLPFC) has been shown to decrease amygdala activation in response to threatening stimuli. Both the rTMS + CPT and sham + CPT groups showed statistically significant improvements in clinician (CAPS) and patient (PCL) rated symptom severity. While rTMS + CPT did better in comparison to sham TMS + CPT, the effect was weaker based on clinician versus patient-rated symptom severity, and the difference was not demonstrated at 9 months. Several upcoming studies look at different techniques of TMS in treatment of PTSD (Table 2). TMS may offer a non-invasive somatic treatment option, as it does not require anesthesia, nor does it require significant post-treatment recovery. Deep brain stimulation (DBS) is being studied in research settings for refractory PTSD. [40]. The subgenual cingulate plays a role in mechanisms of PTSD and has been successfully targeted with DBS for the treatment of depression.

Table 2 TMS studies in PTSD

TMS studies in PTSD
• NCT02981381 synchronized TMS for PTSD and comorbid depressive symptoms
• NCT02158663 randomized trial of 1-Hz- versus 10-Hz right prefrontal rTMS for the treatment of PTSD NCT02158663
• NCT02458521 study of bilateral prefrontal TMS to treat the symptoms of mild TBI (mTBI) and PTSD

Other Non-pharmacologic Considerations

Mishkind et al. [41•] note that with increasing availability of virtual reality consumer products, computer-generated virtual systematic exposure therapy offers a unique treatment option. However, McLay et al. [42], in a 9-week study comparing exposure therapy with and without virtual reality simulator as exposure tool, noted that subjects improved in both the groups, and that there was no significant difference with using a virtual reality simulator compared to control exposure therapy. The virtual reality group had higher dropout rates compared to the control group.

Telehealth revolutionizes access to care in areas with a shortage of mental health providers. VA-DoD PTSD CPG June 2017 found strong evidence for using teleconferencing to deliver trauma-focused therapy. In some areas, telepsychiatry may be the only option for those seeking psychiatric care and may provide greater access for veterans with transportation issues.

Gallegos et al. [43], based on meta-analysis of RCTs of yoga and meditation in PTSD, note that both are potentially useful techniques in treatment of PTSD. Madsen et al. [44•] review the use of integrative medicine in the Military Health System. Integrative medicine has been explored for management of the "polytrauma triad," which includes chronic pain, TBI and PTSD. Some techniques used in this approach include hypnosis, acupuncture, biofeedback, yoga, and mindfulness-meditation. Authors note patient-driven demand for these modalities. VA-DoD PTSD CPG June 2017 found insufficient evidence to recommend any complementary and integrative health practice as a primary PTSD treatment. The work group clarify that they are not against the use of these interventions and acknowledge that in some cases they promote overall recovery and wellbeing.

Conclusion

PTSD often runs a chronic course, with a significant proportion of patients not achieving adequate relief from currently available treatments. Poorly controlled PTSD reduces quality of life and we must seek new treatment options. In this article, we explored some of the potential pharmacological and psychosocial interventions that are on the horizon that may provide new hope for the patient. Shared decision-making processes and patient preference play a crucial role in the overall treatment response.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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