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Novel Therapies for Post-Traumatic Stress Disorder: A Systematic Review

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Abstract

Post-traumatic stress disorder (PTSD) is a psychological disorder that affects about 12 million Americans every year. The main treatments for PTSD are selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Although SSRIs have been shown to produce a response rate of about 60% in patients with PTSD, the complete remission rate is only about 20% to 30%. The SSRIs sertraline and paroxetine hydrochloride are the only two FDA-approved PTSD treat-ments, though they are highly outdated. PTSD is a widely misunderstood disorder that extends far beyond its classification as solely a psychiatric disorder. PTSD has been correlated with elevated levels of gene expression, an overactive immune system, and elevated levels of norepinephrine (NE), all of which contribute to physical and psychological symptoms. This systematic review aims to evaluate novel therapeutic approaches which can be used in concert with psychotherapy to further improve the symptoms of PTSD compared to current treatments.

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Introduction

1.1 Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a psychological disorder that people often experience after a traumatic event, including but not limited to sexual assault, combat, child abuse, and natural disasters[1]. The psychological response to enduring this type of event is not solely panic. The most common lasting effects include insomnia, hyperarousal and hypervigilance, panic attacks, night terrors, depression, anxiety, and physical pain[2]. The first line of treatment for these symptoms, once a diagnosis has been documented, is the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) along with psychotherapy and harmful benzodiazepines[2].

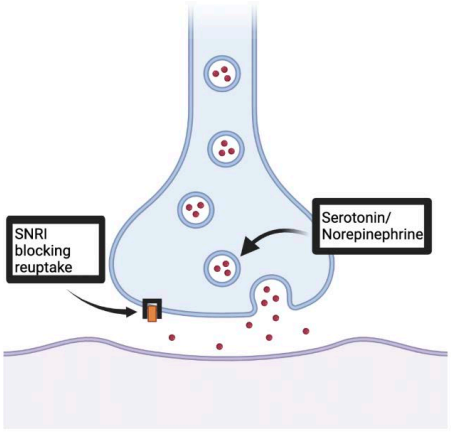

Figure 1. SNRI binding synaptic ion channel, blocking the reuptake of serotonin and norepinephrine.

The pathophysiology of PTSD is complex and includes several neurobiological systems. The hypothalamic-pituitary-adrenal (HPA) axis is a focus of PTSD research because of the involvement of the neurotransmitters in associated pathways[1] as well as the decreased hypothalamus size commonly associated with PTSD. The HPA axis is an intricate neuroendocrine pathway responsible for the stress response and the link between the CNS and endocrine system[1].

1.2 Current Interventions for PTSD

The interventions approved for PTSD show low success rates compared to more novel therapeutic approaches. These are commonly prescribed simultaneously with psychotherapy, exposure therapy, or cognitive processing therapy (CPT)[3].

1.3 Novel Therapeutic Approaches

Novel therapeutic approaches that have been proven to be effective are greatly underutilized in part because they are not FDA-approved for PTSD treatment, meaning that many of these promising treatments are off-label. Off-label use of medication complicates access for individuals looking for therapy as the medication or treatment is often much more expensive. With the expense of off-label medication and the limited FDA-approved treatments, individuals with PTSD are limited in their options.

Hyperbaric oxygen therapy (HBOT) is an approach that is often used for healing large wounds. HBOT has recently been tested on individuals with PTSD without a history of traumatic brain injury (TBI)[4]. Among other brain structures, HBOT has been found to improve hippocampal activity which is responsible for fear extinction, a process those with PTSD often exhibit lower levels of. HBOT can also improve mitochondrial function, induce hyperoxia, and assist in resurfacing memories for those with trauma[4].

Stellate ganglion blocks (SGBs) are injections of local anesthetic, commonly lidocaine or ropivacaine, inserted into the stellate ganglion nerve bundle. Studies have indicated several immediate effects of SGBs, most notably reduced hyperarousal related to the oversensitive fight-or-flight response[5].

Stem cell therapy for PTSD only has one in vitro study testing the efficacy of the treatment, conducted with rats[6]. Though the research is limited, the use of stem cell transplantation for reducing the symptoms of PTSD is promising and warrants further research.

No controlled clinical studies have been completed to evaluate the efficacy of immunotherapy for PTSD specifically[7]. Still, research has been conducted in pain management clinics to track the results and correlation between physical pain from an overactive immune system and the severity of

the psychological effects of PTSD[7]. The use of glucocorticoids and other non-steroidal anti-inflammatory drugs (NSAIDs) aims to reduce pain, and in PTSD patients, the severity of the psychological symptoms is remediated along with physical pain when treated with anti-inflammatory drugs[7].

Topiramate is an anticonvulsant commonly used for epileptic seizures and migraines. Though its widespread use is for neurological disorders, it has also been shown to be effective for psychological disorders such as PTSD and alcohol use disorder (AUD)[8] by acting as a GABA agonist.

1.4 Mechanisms of Interventions

The mechanism of hyperbaric oxygen therapy and its therapeutic effects have been the focus of research now more than ever since HBOT's first use in 1662. HBOT works to induce hyperoxia by forcing 100% oxygen into the bloodstream and surrounding cells[4] instead of the 22% oxygen that is normally perfused under standard atmospheric conditions. The unusual hyperbaric pressure of 100% oxygen on cells can activate or deactivate both oxygen-sensitive and pressure-sensitive genes, which can lead to the effective regulation of gene expression and inhibition of more damage by PTSD[4]. The elevated levels of dissolved oxygen in body tissues contribute to restored mitochondrial function, proliferation and maturation of neural stem cells, and increased neuroplasticity multiple years after injury[4]. It also works to promote anti-inflammatory biological properties. HBOT has been used as a treatment for a variety of disorders and has shown to be effective in many different aspects. However, a main risk of HBOT is oxygen toxicity[8]. Neurological status must be observed throughout the course of treatment because of this possibility. Oxygen toxicity induced by HBOT can manifest in several ways such as tonic-clonic convulsions or oxidative cellular damage[8].

A stellate ganglion block is a single injection of local anesthetic into the stellate ganglion nerve bundle in the cervical spine. This location in the cervical sympathetic trunk has been described as an "anatomical funnel" because it allows the passage of all sympathetic nerve fibers that lead to the thorax as well as to structures of interest in the neck and head[5]. These ganglia provide a connection to the central nucleus of the amygdala and hypothalamus, two of the main nervous structures altered by PTSD. The

SGB injection aims to block the typical hyperarousal during the fight-or-flight response and other high-stress situations[5]. The mechanism by which SGBs function is still unknown, though it may indirectly work by altering levels of norepinephrine (NE) in the brain[5]. Norepinephrine is a key neurotransmitter in the hyperarousal and hypervigilance observed in individuals with PTSD. NE floods the brain when signals arrive in response to sympathetic stimulation and increases the heart rate, alertness, arousal, and amount of energy available to the body. This further contributes to the stress response reported by those with PTSD.

Topiramate is typically used as an anticonvulsant medication though it has recently been tested for its efficacy in reducing PTSD symptoms[9]. Topiramate is an agonist of GABA, an inhibitory neurotransmitter involved in creating inhibitory postsynaptic potentials (IPSPs). Another notable fact is that topiramate blocks glutamate binding[8]. Glutamate is an excitatory small-molecule neurotransmitter that increases action potential firing when it binds to ligand-gated receptors kainate and AMPA. Dysregulation of AMPA receptors (AMPARs) can influence mental health and its effects[10]. AMPARs are dynamic and changes in the quantity of AMPAR at a synapse alter the efficacy of neurotransmitters completing synaptic transmission[10]. Kainate receptors, which share a similar structure and function with AMPA receptors, partly make up nociceptive signaling pathways[11]. Kainate receptor antagonists that target a single subunit (GluK1) have been shown to produce analgesic effects for migraines, indicating their potential use for other painful chronic disorders[11]. Their stimulation not only leads to chronic pain but also increased severity of PTSD symptoms. Because topiramate inhibits glutamate signaling, learning and memory function are often transiently impaired. Over the duration of treatment, however, this impairment is nearly restored[9].

Immunotherapy as an intervention for PTSD is not common practice. The research done on this topic related to PTSD is extremely limited and no relevant controlled clinical trials have been conducted. Because PTSD is classified as a psychological disorder, the main symptoms that are well-defined are behavioral and psychological, not physical. Many individuals with PTSD exhibit elevated levels of several inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor-α, and

interleukin-6[10]. Additionally, autoimmune disorders are often comorbid with PTSD. Though numerous factors can contribute to inflammation, the elevated levels of inflammatory markers indicate a correlation between PTSD and the immune system. Since inflammation can alter neural circuits in brain regions that regulate emotions such as anxiety and fear, a hyperactive immune system causing inflammation can have a detrimental effect on those with PTSD[10]. However, glucocorticoids and NSAIDs have been shown to indirectly reduce PTSD symptom severity through pain relief, providing a basis for further research. Aiming to reduce inflammation, which can restore neural circuits and neurotransmitter activity to normal levels, can help regulate the stress response and overall severity of symptoms[10].

Stem cell therapy is a therapeutic approach that is being investigated for several different disorders, both physical and psychological. For PTSD, there has been one study with stem cells differentiated in vitro that investigated the use of induced human pluripotent stem cells differentiated into neural progenitor cells (iPSC-NPCs)[6]. The iPSC-NPCs are differentiated in a laboratory before being transplanted into the rat model brain. Once they are transplanted as neural progenitor cells, symptom severity can be evaluated throughout the course of treatment. As cells mature in the brain, they can reverse hippocampal tissue damage, promote regeneration, and induce motor function recovery in rat models of PTSD[6]. Adapted assessments were performed on the rat models that showed similar responses to stimuli as humans with PTSD. At the end of treatment, it was found that iPSC-NPCs can reduce symptom severity, specifically the fear response, and reverse the physical neural damage that PTSD causes[6].

1.5 Outcomes

The clinician-administered PTSD scale for DSM-5 (CAPS-5) is a 30-item interview that can give clinicians and clinical researchers more information about an individual's past history of PTSD, present symptoms, symptom severity, and more[12]. Questions aim to assess the impact of PTSD symptoms on daily activities, including one's social and occupational life. The scale can also classify a subject within the dissociative subtype as well as assess the overall PTSD severity and symptom improvement[12]. For the studies

included in this review, the CAPS-5 is a common outcome used to evaluate the efficacy of an intervention. Another outcome assessment includes the brief symptom inventory-18 (BSI-18) which questions the subject on three symptom scales: depression, anxiety, and somatization. Furthermore, the Beck Depression Inventory-II (BDI-II) is a widely used and accepted psychometric test to assess the severity of depression in a subject and includes 21 multiple-choice questions along with a self-reported inventory about recent feelings, emotions, and well-being[13]. In addition to these tests, several imaging techniques were used including fMRI and diffusion tensor imaging-fractional anisotropy (DTI-FA), which evaluates the white matter microstructures in the brain. For non-imaging tests, higher scores are associated with more severe symptoms[12]. What warrants significant changes in CAPS-5 scores changes with the study, though it is commonly a change of 10 points that indicates significant improvement or deterioration.

1.6 Objective

The objective of this paper is to qualitatively analyze the efficacy of these five interventions for PTSD. This analysis is based on several clinical trials, randomized control trials, in vivo and in vitro studies, and one review paper.

1.7 Method

This systematic review follows the standard principles for search strategies. A comprehensive search using PubMed was performed on September 16th, 2022. Another search was performed on October 12th, 2022 to ensure that all relevant articles are being utilized. This search included published manuscripts and abstracts. The two abstracts provided useful information pertaining to these therapeutic approaches, warranting their inclusion. The PubMed search included the following terms: post-traumatic stress disorder[MeSH], PTSD[MeSH], stellate ganglion block[MeSH], hyperbaric oxygen therapy[MeSH], topiramate[MeSH], immunotherapy[MeSH], and stem cell[MeSH]. The Boolean operator used in these search terms is ‘and’. Included are all primary research studies that are published. There are five interventions with both in vivo and in vitro studies being considered. All included studies are relevant to the topic and published in English. This systematic review is from the latest studies published related to PTSD and its interventions. Each study is screened by

two group members. The key elements of the study design were assessed and reported for each study, including clinical trials, randomized clinical research studies, and in vivo studies. The snowballing technique was also used to acquire additional articles through citations in previously included articles.

After applying the search strategy stated above, 9 stem cell studies, 3 stellate ganglion block studies, 1 topiramate study, 1 immunotherapy study, and 11 hyperbaric oxygen therapy studies were found. After applying the snowball technique, 14 studies have been included in this paper based on relevance and inclusion criteria. This includes 1 stem cell study, 1 immunotherapy study, 6 stellate ganglion block studies, 4 hyperbaric oxygen therapy studies, and 2 topiramate studies. Endpoints include the effects of hyperbaric oxygen therapy, stellate ganglion blocks, topiramate, immunotherapy, and stem cell therapy on PTSD symptoms severity.

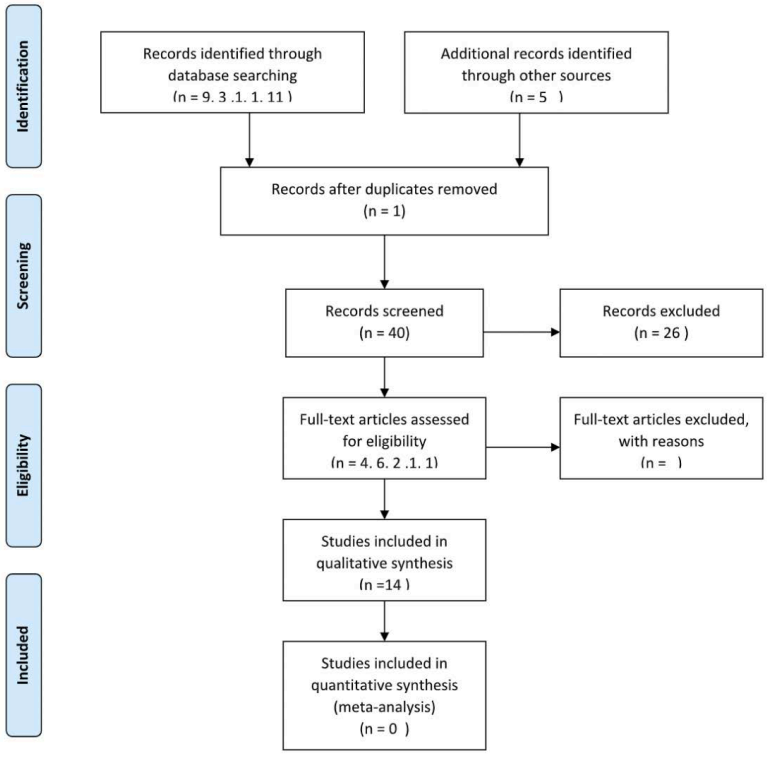

Figure 2. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).*

Results

2.1 Hyperbaric Oxygen therapy

A US military-sponsored, randomized clinical trial was conducted in 2018, testing the effects of hyperbaric oxygen therapy (HBOT) on 71 participants with PTSD and/or a traumatic brain injury (TBI)[14]. The participants were randomized to either the treatment group (n=36) or the sham group (n=35), and at baseline, 49% of participants met PTSD criteria. The primary outcome of this study was the Neurobehavioral Symptom Inventory which was assessed at baseline, 13 weeks, and six months, in addition to several other indicators of PTSD symptom severity and neurocognitive tests[14].

This study administered daily one-hour sessions, 5 days a week, for 40 sessions total. The treatment group received >99% oxygen at 1.5 atmosphere absolute (ATA) while the sham group received regular air at 1.2 ATA (25% oxygen). The sessions were completed within 12 weeks.

The participants in the HBOT group were all older with more combat deployments, exhibiting worse anger control and more frequent traumatic axonal injury[14]. Though these may indicate that the treatment group encountered worse brain injuries, the baseline post-concussive and PTSD symptom scores were similar to the sham group. The Rivermead Post-Concussion Symptom Questionnaire (RPQ) total, RPQ-13, and PTSD Checklist-Civilian Version hyperarousal scores showed more severe symptoms in the treatment group at baseline[14].

At 13 weeks, univariate and longitudinal analysis was used to assess symptoms based on the outcomes. The RPQ-3 domain, which includes headaches, dizziness, and nausea, was improved compared to the sham group (p=0.01). The Neurobehavioral Symptoms Inventory total score and affective domain change scores indicated success in the treatment group compared to the sham group, but only using univariate testing. At 13 weeks, several tests indicated an improvement in anger subscores with both univariate and longitudinal assessment but the results were not statistically significant[14]. Additionally, at 13 weeks and 6 months, 19 out of 36 participants in the HBOT group reported feeling the benefits of HBOT versus 10 out of 33 participants from the sham group. At 6 months, 19

participants from HBOT and five participants from the sham group reported the same effect. Other neuropsychological tests were performed, with improvements for the HBOT group at 13 weeks, but most did not reach statistical significance. However, the sham group never exhibited statistically significant results in any total or subscore assessments at 13 weeks[14]. With all of these analyses, participants who had PTSD had larger improvements than those without PTSD. Furthermore, participants without PTSD had no significant improvements in both the treatment and control groups[14].

This indicates that HBOT may work better as a treatment for PTSD as opposed to TBI. By 6 and 12 months, any distinct differences between groups had diminished, with improvements at six months no longer being significant as they were at 13 weeks. Both post-concussive and PTSD symptoms were worse at 12 months post-HBOT compared to baseline for participants in both groups. HBOT participants improved on six out of seven California Verbal Learning Test-II subtests compared to the sham group at 13 weeks, and two subtests reached statistical significance in univariate and longitudinal assessments. By 6 months, most score differences between groups were no longer statistically significant. Sleep issues within the HBOT participants exhibited improvement at 13 weeks, but the results between groups were not significant. Both groups also reported improved sensory organization scores. In addition to these outcomes, participants with PTSD who received HBOT were able to walk further in the six-minute walk test after treatment at 13 weeks[14].

These results indicate that HBOT may be better utilized as a treatment for PTSD rather than post-concussive symptoms or TBI symptoms. Furthermore, this study exhibits findings that support long-term treatment of HBOT to keep symptoms reduced for longer. Though many of the findings were not statistically significant, those with PTSD showed more improvement than participants without the disorder, warranting further research on the use of HBOT for PTSD. This study was quite small with about an equal number of participants in both groups.

Additionally, all of the participants were military personnel which limits generalizability to other populations of individuals with PTSD. Further

analysis needs to be done on HBOT for PTSD because of the lack of statistical significance in this study though it did show to alleviate PTSD symptoms more than TBI symptoms.

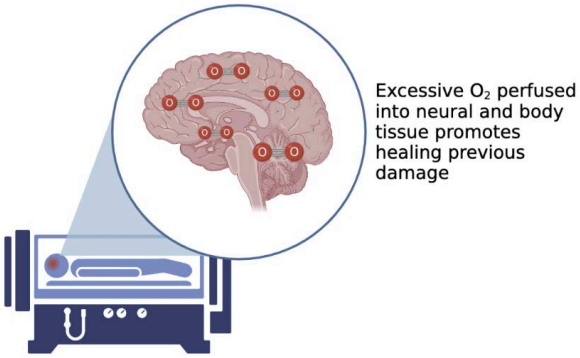

Figure 3. *HBOT induces hyperoxia, causing excessive perfusion of oxygen into the bloodstream and neural and body tissue.*

A randomized case-control study published in 2022 completed a hyperbaric oxygen therapy study on 29 veterans with PTSD[4]. Compared to the control (n=15), the treatment group (n=14) showed significant improvement in CAPS-5 scores by the end of the trial. The study focused on male veterans aged 25-60 who had treatment-resistant PTSD with debilitating symptoms for at least four years prior.

Participants underwent baseline evaluation which included brain imaging and psychological interviews by clinicians. The participants also completed an evaluation three months after HBOT or control exposure. The HBOT was administered in concert with the subjects' pre-trial psychotherapy. The participants underwent 60 daily sessions, five days a week. During each HBOT session, the treatment group was exposed to 100% oxygen at 2 ATA with a five-minute break every 20 minutes.

The primary objective of this study was a change in CAPS-5 score compared to baseline evaluations. The secondary objective included the BSI-18 and BDI-II questionnaires. Other outcomes included imaging data acquisition which measured gradient-echo blood oxygen level-dependent contrast

sequences. A functional task design, in which participants had to perform a memory recall test, was also used to test their results.

CAPS-5 Subcategories	Baseline Scores	Post-HBOT Scores (n=14)	Baseline Scores	Control Scores (n=15)
Avoidance symptoms	4.5 ± 1.7	2.3 ± 1.8	4.5 ± 1.8	5.0 ± 1.4
Arousal and reactivity symptoms	12.3 ± 4.5	9.0 ± 5.6	15.3 ± 3.2	15.9 ± 3.6
Cognition and Mood Symptoms	17.5 ± 3.7	11.1 ± 7.4	16.8 ± 5.6	17.5 ± 3.8
Intrusion Symptoms	12.2 ± 3.8	6.6 ± 4.7	12.9 ± 2.6	13.2 ± 2.1
Total Scores:	46.6 ± 11.5	28.5 ± 17.4	49.5 ± 10.7	51.5 ± 8.4

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for DSM-5, HBOT, hyperbaric oxygen therapy
Table 1. CAPS-5 scores for the treatment arm and control group at baseline and post-HBOT/control exposure

Table 1 indicates the significance of results in the treatment arm ($p<0.0001$) compared to the control group, which didn't improve in any subscores or total score[4]. Similarly, BSI scores ($p=0.024$) as well as BDI scores ($p=0.01$) significantly improved[4]. In the HBOT group, there were improvements in group-time interactions in frontal white-matter fiber bundles that connect the thalamus and frontal lobe. There were also improved clusters found in parietal white matter and the anterior limb of the internal capsule and cerebral peduncle. The same patients in both groups were used for task-related functional imaging, and there were no significant functional differences between the fMRI images except for improved activity after HBOT in several regions of the brain including the hippocampus[4].

This study is limited by its size with only 35 randomized patients. Additionally, there was no blinding for either group. The results of this study support the fact that HBOT is highly effective in treating PTSD symptoms based on CAPS scores and brain imaging. There is evidence that this treatment should be more widespread, though it is limited by the fact that HBOT is a historically difficult treatment to be covered by insurance and it requires specialized physicians to perform and oversee the treatment. Hyperbaric oxygen therapy has revealed the pressure-sensitive and oxygen-sensitive genes involved in the etiology of PTSD. These genes could

be further investigated and possibly manipulated with gene therapy, though this has not been done yet.

In addition to these trials, an observational cohort study was conducted to investigate any persistent post-concussive symptoms (PCS) in participants from two completed United States military trials of hyperbaric oxygen therapy (HBOT). Individual changes varied widely, ranging from -23 to +28 points[15].

2.2 Stellate Ganglion Block

Stellate ganglion blocks were first used to treat PTSD in 2010[16]. They have been used to treat dysautonomia, vasomotor symptoms, pain in the upper extremities, and most recently, psychiatric disorders. The first multisite, randomized clinical trial of stellate ganglion block effects on PTSD symptoms severity was published in February 2020[16]. This trial pulled participants from three US Army Interdisciplinary Pain Management Centers which included active-duty service members as the first inclusion criteria. The participants were randomized 2:1 to a sham group (n=39) or treatment group (n=74), and baseline characteristics were similar in both groups based on mean CAPS-5 scores[16]. Participants were administered a right-sided SGB at 0 and 2 weeks, and they were assessed at 0 and 8 weeks post-injection. The injections were performed using ultrasonography. 7-10 mL of 0.5% ropivacaine was administered to the treatment group and the sham group received 1-2 mL of normal saline at the same anatomical location, the C6 anterior tubercle[16]. Measures were taken so as to not unblind participants due to the difference in medication and medical instruments, and conversations were scripted for medical personnel who were not blinded.

The primary outcome of this trial was a decrease in CAPS-5 total symptom severity scores (CAPS-5 TSSS), indicating improvement. This assessment ranges from 0-80 points, with higher scores indicating more severe PTSD symptoms and a 10-point change per individual indicating the results as significant and clinically meaningful[16].

Total symptom severity scores for the Clinician-Administered PTSD scale for the DSM-5 (CAPS-5)	Treatment Arm, unadjusted scores (n=74)	Sham Group, unadjusted scores (n=39)
Baseline Scores	37.61	39.82
Scores at 8 weeks	25.67	33.68
Total Score Change	-12.16	-5.79

Table 2. Total symptom severity scores, assessed by the CAPS-5, at baseline and 8 weeks for the treatment and sham groups.

Table 2 highlights the overall trend of improvement for the treatment arm as well as the sham group. Though both groups improved by some amount, the treatment group had a greater overall decrease in symptom severity scores, though not statistically significant. However, there were clinically significant improvements in subsets of PTSD-symptom assessments, including but not limited to depression and distress[16].

This study heavily supports the use of SGB injections for those with PTSD as a way to significantly reduce the most common and detrimental symptoms of PTSD. Limitations of this study include unblinding of the participants in the treatment arm due to the onset of Horner's syndrome. This is a side effect and indication of a successful injection in which there is a disrupted nerve pathway going from the brain to the face, resulting in a smaller pupil on the affected side, a drooping eyelid (ptosis), and a reduction in sweat[16]. The medical personnel performing the procedure on the participants were also unblinded to ensure the safety of the participants, though their interactions were limited and scripted. Other limitations include generalizability, as this study only included active-duty military personnel with only 10 females and 3 females in the treatment and sham groups respectively.

Because of the limited studies done on this intervention as a treatment for PTSD, there is little evidence of whether a right-sided SGB or left-sided SGB is more effective with the use of fluoroscopy versus ultrasonography, or if they produce the same results. In 2021, however, a cadaveric study was performed and published testing vertebral body spread of the injectate based on sidedness[17]. Ten soft-cured human cadavers were administered both fluoroscopic and ultrasound-guided injections each. The injection was a

mixture of 7 mL of omnipaque and methylene blue and was used as the injectate on both sides. The cadavers were then dissected to visualize the staining of the sympathetic trunk associated with methylene blue[17]. The primary outcome was the staining of methylene blue at the cervical sympathetic trunk upon dissection.

The secondary outcome was a craniocaudal spread of the dye. After performing two injections on each cadaver for a total of 20 injections, they were dissected. Fluoroscopic guidance of SGB injections had a successful stain rate of 60%, six out of ten cadavers[17]. For the ultrasound-guided SGB, the successful stain rate of the sympathetic chain was nine out of ten for a 90% success rate[17]. The failed injections were because the injections were administered in the wrong location, such as the carotid sheath and within or beneath the longus Colli muscle, instead of the stellate ganglion nerve bundle at the C6 anterior tubercle[17]. The study found no statistically significant differences in approach using fluoroscopy versus ultrasonography, though there was greater staining using ultrasonography.

Limitations of this study include the fact that it was performed on cadavers which may not accurately represent the spread of injectate in living subjects. The fascial layers play a large role in the spread of injectate, and the compositional properties of the fascial layers in cadavers are altered compared to living humans. In addition, no functional outcomes can be assessed on cadavers.

A study examining clinical endpoints in people with PTSD was completed in May of 2013, analyzing 1,462 data points from the PTSD Checklist-Military (PCL-M)[18]. This study analyzed the data points of 26 patients in a military clinic, all of whom had several combat deployments that consisted of receiving and returning direct fire. The subjects were all male ranging in age from 29 to 45. The participants were administered 7 mL of 0.5% ropivacaine injected over two minutes, and a successful injection was indicated by the presence of Horner's syndrome.

The primary outcome, PCL-M score, was tested at baseline and at two follow-up appointments[18]. The 16-point decrease in mean PCL-5 score is significant ($p<0.001$), but the mean score at the second follow-up did not show significant improvement from 1-week post-injection.

Baseline Mean PCL-M Score	Mean PCL-5 Score at 1-Week Follow-Up	Mean PCL-5 Score at 2-4 Month Follow-Up
48.69	32.15	31.88

Abbreviations: PCL-5, PTSD Checklist for DSM-5

Table 3. Change in mean PCL-5 score from baseline through subsequent follow-ups.

All three symptom cluster scores were significantly improved ($p<0.001$) one-week post-injection, except for one item in a single cluster[18]. These results support the use of SGB injections for military personnel who suffer from combat-related PTSD. The limitations of this study are similar to others: many studies for PTSD generally test on active-duty personnel or veterans only, as well as specifically men of certain age ranges and ethnicities. This limits generalizability for other PTSD-affected populations including women, children, and civilians who have never served in the military or have experienced combat.

In addition to the cadaveric study and in vitro trials, an in vivo study done on rats was conducted and published in 2021[19]. This study differs in that it tested the effects of PTSD-related sleep deprivation on memory dysfunction and hippocampal injury. Sleep deprivation is a common symptom of PTSD because of insomnia and night terrors. Sleep deprivation can detrimentally affect the brain and the body and lead to a cascade of other symptoms.

It has been found that sleep deprivation is associated with cognitive dysfunction, which is mediated through melatonin[19]. Stellate ganglion blocks have been found to exhibit similar effects as those of therapeutic interventions with melatonin in that they prevent the breaking of cervical sympathetic preganglionic fibers, reduce sympathetic nerve tension, and help regulate the balance in multiple body systems, including the autonomic nervous system, endocrine system, and immune system. Sleep deprivation has also been shown to impair hippocampal coding activity, cause hippocampal mitochondrial dysfunction, neurodegeneration, microglia activation, and neuronal apoptosis in the hippocampus[19].

Furthermore, there has been confirmation of increased white blood cell counts and inflammatory factors, including C-reactive protein (CRP), IL-1β, IL-6, and TNF. There are also decreased serum melatonin levels[19].

This study tested whether alleviating the hippocampal tissue damage can improve spatial learning and memory dysfunction caused by sleep deprivation in a rat model of PTSD. 65 male Sprague Dawley rats were randomized to four different groups. These groups were control, sleep deprivation (SD), SGB, and SGB + SD (n=16). The SGB and SGB + SD groups were administered one right-sided stellate ganglion block once per day. The SD and SD + SGB groups were subjected to a multi-platform water environment for 96 hours to induce sleep deprivation. Their body weights were also analyzed at this time. The Morris water maze was used to detect the spatial learning and memory function of rats. The escape latency, the time it took from the rats entering the water to finding the security platform, was measured as an outcome. After the water maze, eight rats each had 3 mL of inferior vena cava blood samples analyzed for serum melatonin content.

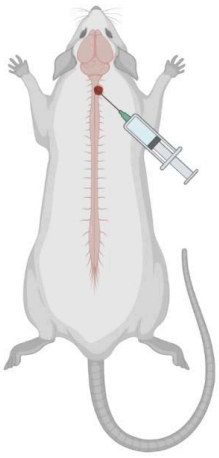

Figure 4. *0.2% ropivacaine is injected into the anterior cervical spine of the rat.*

The SGB and SGB + SD groups were given a right-sided SGB six days prior to sleep deprivation induction up until the end of the day, with one SGB of 0.2 mL of 0.2% bupivacaine per day. The onset of Horner's syndrome indicated that the injection dissipated into the correct anatomical area. Rats in the SD group were given the same volume of normal saline, and the control group was not treated. After the injections were administered, the

escape latency time of the SD group was significantly longer compared to the control group. The SD + SGB group was shortened, and the escape latency in the SGB and control groups tended to be consistent[19]. The number of rats that crossed the platform was much lower in the SD than in the control group ($p<0.05$), and those in the SD + SGB was significantly higher compared to the SD group ($p<0.05$)[19]. The platform was removed and resident time and frequency of crossing the platform were recorded. The SD + SGB group showed higher crossing and resident times in the test compared to the SD group.

The body weight of the rats in the SD group was reduced compared to the control group. The SD + SGB group showed significantly increased body weight after injection compared to the SD group. In comparison with the control group, there was no significant distinction between IL-6, IL-1β, and serum MT content in the hippocampus of the rats in the SGB group.

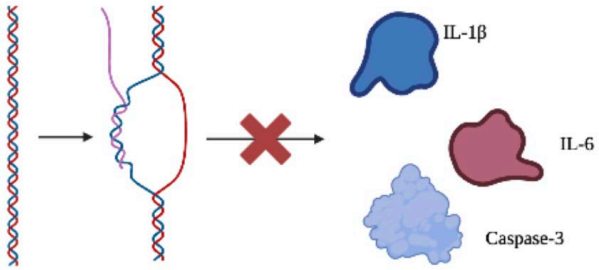

Figure 5. *Gene expression of inflammatory and apoptotic proteins is decreased after treatment. This reduces excessive cell death common in individuals with PTSD.*

However, there were elevated levels of IL-6 and IL-1β content in the hippocampus of SD rats compared to the control. A Western blot of the relative expression of Caspase-3 protein in SD rats' hippocampus was significantly higher, and the relative expression of the same protein in the hippocampus of SD + SGB rats was significantly lower with no difference in the protein's expression between SGB and control groups[19]. Histological analysis of hippocampal tissue showed that the stress damage and the

number of hippocampal neurons that were injured in the SD group were very elevated, most prominent in the vertebral neurons in the hippocampal CA3 region. The vertebral cells were decreased in size, irregular, loose, and fuzzy. The neuronal damage in the SD + SGB group was significantly improved compared to the control group, and the cells were more ordered with a clearer structure.

In addition, the serum MT levels decreased with more sleep deprivation. The serum MT content significantly improved in the SD + SGB group, indicating that a right-sided SGB can alleviate the decrease in serum MT secretion secondary to sleep deprivation. The elevated IL-6 and IL-1β levels caused by sleep deprivation are pro-inflammatory cytokines, indicating that right-sided SGBs can inhibit the initial inflammatory reaction after trauma exposure[19]. They can also be used to inhibit the excessive inflammatory reaction after TBI, preserving brain function.

The Caspase-3 protein that was found in elevated levels in SD rats was reduced after SGB, further indicating that the excessive apoptosis can be alleviated as evidenced by the fact that CA3 protein levels were reduced in the SD + SGB group[19]. Furthermore, the degree of stress damage on hippocampal neurons was significantly reduced in the SD group. Though these are all post-injury alleviating factors, the behavioral platform used in this experiment showed that prophylactic administration of SGB can provide preventative treatment for spatial learning and memory dysfunction[19].

The results of this experiment make it highly evident that SGB injections produce several significant benefits such as increased melatonin production and secretion, alleviation of hippocampal apoptosis due to decreased Caspase-3 protein levels, spatial learning and memory dysfunction improvement, and hippocampal neuron regeneration after damage. Given that this is a non-invasive, generally safe treatment, SGBs should be further investigated and utilized based on this experiment done in the rat model.

In addition to these studies, a cohort of behavioral clinicians was interviewed about their thoughts on the efficacy of SGB for trauma-related disorders[20]. Approximately 50 mental health providers were sent an 18-item survey to assess their experiences with SGB as a treatment for trauma-related

conditions. Of the 27 clinicians that responded, 23 had input that was used in this study (10 psychologists, 7 psychiatrists, 4 licensed clinical social workers, and 2 psychiatric nurse practitioners). Experience with SGB varied between providers. The survey showed that 95% (22 out of 23) of providers would recommend the use of SGB to a colleague while 65% said this procedure is very beneficial[20]. 30% indicated SGB as somewhat helpful and over 80% were likely or very likely to refer a patient to get an SGB procedure. 96% of the providers also responded that SGB is most helpful for arousal and reactivity compared to other symptoms[20].

This cohort responded that SGB is at least as beneficial as other heavily used interventions, with 100% responding that SGB is very beneficial or somewhat beneficial. None of the respondents said that SGB is harmful or not helpful[20]. Furthermore, SGB was overall favored over each of the 8 interventions endorsed for PTSD in the Clinical Practice Guideline[20].

Both qualitatively and quantitatively, the overall results of studies assessing the efficacy of SGB as an intervention for PTSD support their use for widespread treatment. SGBs are highly beneficial with minimal risks and side effects. The main side effect is Horner's syndrome which subsides a couple of hours post-procedure when the local anesthetic has worn off and also acts as an indicator to clinicians that the injection was successful[16]. This, in addition to the fact that this is non-invasive, quick, and has immediate beneficial effects, can help increase treatment adherence rates, thereby also improving the number of those with PTSD who can benefit from this treatment over others.

Because of the sheer number of veterans and active military personnel that suffer from this disorder, all of the conducted studies have been limited to veterans, mainly Caucasian men aged 18-65. This limits generalizability for others that PTSD affects including sexual assault victims, those who have experienced natural disasters or other non-combat-related trauma, women, children, and people of other ethnicities. Furthermore, the Department of Defense is the main source of funds for these clinical trials. This forces the trials to only include those who are serving or who have served in combat. Due to this, funding outside of the DoD needs to be identified to carry out trials on non-military civilians who suffer from PTSD.

Future applications of SGBs are limited given these trials. In order to make this treatment more mainstream and widespread, there can be increased and more diverse populations in clinical trials, more in-depth research, training of physicians outside of military hospitals and clinics to perform this procedure, and better analysis of complete data sets. Overall, this is a highly effective treatment that is limited by its research and the training of physicians as well as funding for trials and insurance coverage for patients. It has been shown to increase melatonin levels to combat insomnia, regulate gene expression, decrease hippocampal apoptosis, reverse hippocampal damage, improve spatial learning and memory, and decrease depression, anxiety, hyperarousal, and hypervigilance[5, 16, 18, 19, 20], making this a target for further application. The numerous beneficial effects of SGBs warrant further research and application, especially for those outside of the military.

SGB can be used to target the expression of Caspase-3 protein, IL-1β, and IL-6. Targeting these proteins can aim to reduce highly damaging hippocampal tissue reduction and neuronal degeneration, along with reducing inflammation in the brain and body immediately following a traumatic event because of the pro-inflammatory properties of IL-1β and IL-6 genes. Further research on the effects of SGB on gene expression is warranted because of these proteins' roles in PTSD symptom severity. Western blot assays should be utilized in further studies to assess this as this has only been done in a rat model.

2.3. Topiramate

Topiramate, a medication commonly used to treat migraines and epilepsy, is a second-generation anti-epileptic drug[21]. Though the precise mechanism is unknown, it is known that the drug blocks voltage-gated sodium channels, which are thought to control depolarization during seizures. It reduces membrane depolarization with AMPA and kainate receptors[10, 11] while also enhancing GABA receptor activity. Additionally, it is known to be an inhibitor of carbonic anhydrase and NMDA receptor activity, allowing for partial regulation of seizures in the brain[21].

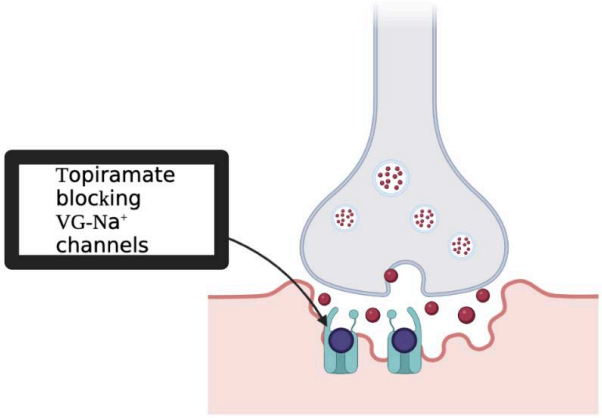

Figure 6. *Topiramate blocks sodium channels to reduce impulses sent across neural synapses.*

An in vivo study was conducted with 30 veteran patients suffering from PTSD and alcohol use disorder, in which patients were placed in two groups, treatment or placebo (negative)[9]. There was a 12-week double-blind treatment administered in which half the patients (randomized) were given increasing doses of topiramate from 25 mg on day 1 up to 300 mg a day by week 6, and constant doses through week 12. Participants in the negative control group were given a placebo treatment.

The primary hypothesis of the difference between the tested topiramate group and placebo group was tested using a statistical t-test, which produced a p-value=0.019 that indicated statistically significant results in the difference between these two groups and their drinking days per week[9]. The main effect of the treatment for those who received it was reduced standard drinks per week, which decreased by 55% for the topiramate group along with a 61% reduction in drinks per day[9].

An additional in vivo study analyzed efficiency of topiramate treatment on post-traumatic stress disorder patients from the clinic of the violence program of Federal University São Paulo City[22]. This was another 12-week double-blind treatment test where 35 patients were randomly assigned to the treatment group or negative control group. The Clinician Administered

Post-traumatic Stress Scale (CAPS) and Beck Depression Inventory (BDI) were used as primary indicators of results[22]. The mean topiramate dose administered was 102.95 mg a day.

The study yielded 82.35% of patients with significant improvements in their CAPS-B score, seen with improvements in re-experiencing symptoms such as flashbacks, intrusive memories, and nightmares of the trauma ($p = 0.04$)[22]. There was also a significant improvement in avoidance/numbing symptoms associated with trauma, social isolation, and emotional numbing in CAPS-C scores ($p = 0.0001$). Additionally, there was a significant decrease in CAPS total score for the experimental group when compared with the placebo group ($p = 0.0076$)[22].

The first study analyzed a high ratio of male participants with barely any female subjects. This made results highly biased towards male patients, and further research may have to be done to gauge if the results can be generalized to female patients due to differences in PTSD manifestation between genders. However, the second study saw similar improvements in CAPS scores with a majority of the participants being women, at 21 out of 35 patients.

Additionally, the study focused on PTSD patients that were veterans. We cannot generalize these effects to other populations struggling with post-traumatic stress disorder since the studies were concentrated on veterans suffering from symptoms. Furthermore, the majority of participants in the first study were white. More research concentrating on different races can help broaden the spectrum of participants that gain positive results following the treatment of topiramate.

For both studies, only 30-40 patients were observed, and with such a small sample size, the results are less accurate. More studies conducted with greater sample sizes will increase the significance of the results.

Though already being widely used as a drug to treat neurological illnesses such as epilepsy or migraines, further studies regarding the dosage of topiramate to treat post-traumatic stress disorder are proven to produce positive results. The main risk is topiramate may also produce adverse effects when taken in larger doses, with the most common side effects in migraine

patients being insomnia and drowsiness. However, it is known as a relatively safe drug. It should be avoided in patients prone to experiencing metabolic acidosis due to being a carbonic anhydrase inhibitor[21]. With the already significant results seen in topiramate decreasing post-traumatic stress disorder indicative diagnosis, including CAPS score, BDI score, and PTSD Symptom Severity scores, further studies conducted on a larger and more diverse sample group can give support in popularizing this method for post-traumatic stress disorder patients.

2.4. Stem Cell Therapy

Stem cell therapy and transplantation have been used widely since their first application in 1957[23]. Stem cell transplants are mainly used to target damaged cells from chemotherapy or diseases usually related to cancer. Stem cell therapies are of particular interest because of the vast results they have the potential to produce. The application of stem cell therapy for trauma-related disorders such as PTSD has not yet been explored in humans. The only research done on this topic consists of a single in vivo study published in 2021[6].

The 2021 study used induced pluripotent stem cells (iPSCs), generated by reprogramming somatic cells by inserting certain genes. iPSCs can be differentiated into any cell type[6]. Among the various types of cells, induced pluripotent stem cell-derived neural progenitor cells (iPSC-NPCs) can replace lost neurons that have degenerated in a highly specific region of the brain. They can replace the loss of neurons in the hippocampus and regenerate impaired hippocampal structure, and there is accumulating evidence that iPSC-NPCs can support tissue repair and functional recovery after neurogenic injuries[6].

In this study, male Sprague Dawley rats were used as subjects. Cell culturing of iPSCs was done in an embryonic stem cell medium until typical human embryonic stem cell morphology was present. The stem cell colonies were then dissociated. The rats were randomized to six groups (n=8) on days 7, 14, and 21. On day 7, the groups included control, PTSD, PTSD + PBS, and PTSD + iPSC-NPCs. On days 14 and 21, the group was PTSD + iPSC-NPCs. 14 days after the initial injury, iPSC-NPCs were transplanted

into the hippocampal site[6]. At different points in time, the rats' brains were dissected for analysis.

The open field test was used to evaluate outcomes related to locomotor activities. The fear conditions test was used to subject the rats to a tone-foot-shock pairing. The induced pluripotent stem cells were allowed to develop for 24 days in the laboratory to ensure differentiation. Seven days after transplantation, there was no significant difference between the control and transplant groups in residence time and behavior modification[6]. This indicates that short-term transplantation does not affect locomotor activity or anxiety. Long-term treatment was shown to be effective 14 and 21 days after treatments, with increased residence time and behavior modifications indicating lowered levels of anxiety and depression[6]. This also supports that long-term treatment improves and regulates cognitive dysfunction.

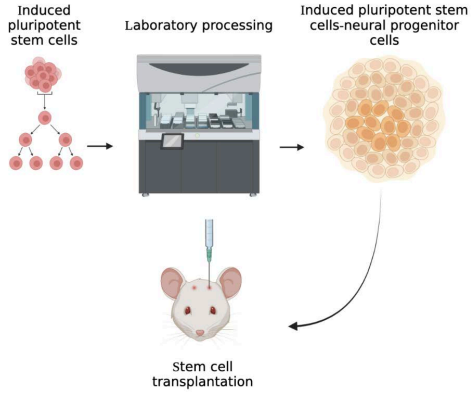

Figure 7. *Human induced pluripotent stem cells can be differentiated into neural progenitor cells following laboratory treatment, and can then be transplanted into the brain of the rat.*

Furthermore, neuronal nuclear protein (NeuN) was used as a marker of mature neurons in immunofluorescence assay. This suggested that iPSC-NPC transplantation can increase neurogenesis in the damaged hippocampus found in PTSD[6]. In addition, immunostaining indicated that transplantation can increase astrogliosis, thereby minimizing damage to CNS injuries. In another Western blot analysis, there was a reduction in BDNF expression which was reversed after 14 and 21 days in the transplant group. This suggests that transplantation supports functional recovery through upregulating BDNF[6].

The results of this study indicate that iPSC-NPC transplantation after NPC treatment in vitro can promote neurogenesis and functional recovery, reduce anxiety and depression, and repair damaged hippocampal tissue and neurons[6]. The limitations of stem cell transplantation as an intervention for PTSD are numerous. This is the only study that has been done on this intervention for PTSD, and it is only in a rat model, not in humans. The results of long-term transplantation indicate that further research is needed before it can be considered a viable treatment option. Stem cell transplants are also limited because of the high risk of developing neoplasms, so the cells must be treated carefully before transplant. Though this may seem like an intense treatment for PTSD, there is promise that it can be beneficial in reducing symptoms and physiological damage.

2.5 Immunotherapy

PTSD is often comorbid with a number of inflammatory diseases and autoimmune disorders[7.] Though many factors can play a role in inflammation unrelated to trauma, there are elevated rates of immune-related conditions in those with PTSD. A review published in 2022 assessed the use of anti-inflammatory drugs for reducing PTSD symptoms and their mechanism within the disorder[7]. Though the directional relationship between PTSD and inflammation is unknown, accumulating evidence points to the adaptive and innate immune systems' roles in the pathophysiology of PTSD. There are often variations in peripheral inflammatory markers in those with PTSD including C-reactive protein, IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α)[7]. There have also been several genomic studies that have identified multiple genes related to the immune system that are altered in those with PTSD. More specifically, transcriptomic studies performed on US marines showed the upregulation of immune-related genes and the overexpression of genes related to the innate immune response. Interferon signaling pre-deployment was able to predict post-deployment PTSD[7].

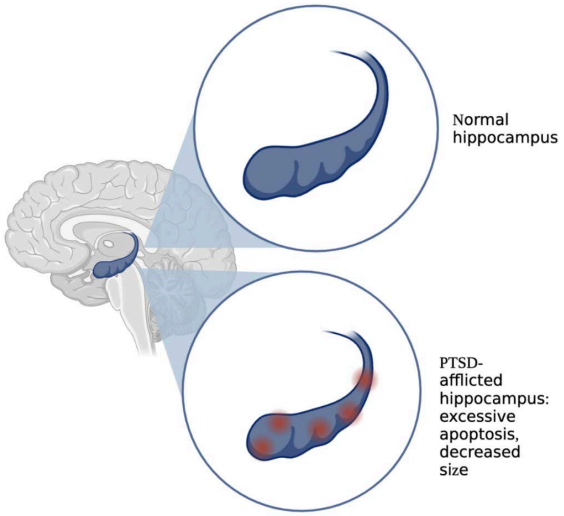

Figure 8. *PTSD induces hippocampal atrophy and excessive apoptosis, leading to a much smaller and inflamed hippocampus.*

PTSD is associated with variations in regions of the brain that regulate fear, anxiety, and threat detection. These regions mainly consist of the amygdala, hippocampus, and hypothalamus. Upon stress, people with PTSD have heightened amygdala activation and increased pro-inflammatory cytokine levels[7]. This is associated with depression, social disconnection, fatigue, and cognitive disturbance, which often come with PTSD. The hippocampus, which is involved in fear and memory processing, is often found in smaller volumes in those with PTSD. A smaller hippocampus is associated with increased inflammation. In a rat model, it was found that inflammation of the hippocampus suppresses neurogenesis and stimulates apoptosis of neuronal progenitor cells, indicating that inflammation of the hippocampus may greatly contribute to cognitive and emotional issues that come with PTSD. Several more peripheral structures are affected by inflammation and PTSD, which affect neurotransmitter release and reuptake, again correlating the emotional issues of PTSD and inflammation[7].

Of the two FDA-approved SSRIs, none target inflammation. There are several proposed potential treatments in this review that target the inflammation associated with PTSD, though none are FDA approved for PTSD treatment. Monoclonal antibodies are approved for the treatment of

autoimmune disorders and cancers[7], and the elevated levels of IL-1β, IL-6, and TNF-α give reason to believe that blocking these pro-inflammatory cytokines using monoclonal antibodies could better regulate gene expression and reduce inflammation. Though there are no studies on this intervention for PTSD, several TNF inhibitors have been reported to reduce anxiety and depression in people with psoriasis, indicating the potential application of TNF inhibitors for other diseases that cause inflammation[7].

Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) inhibitors can regulate the pro-inflammatory cytokine production in the body, thereby directly reducing inflammation[7]. Celecoxib, a COX-2 inhibitor, was able to reduce depression symptoms in people with major depressive disorder, meaning it potentially reduced IL-6 levels, one of the upregulated genes in people with PTSD. Ibuprofen, an NSAID, reduced anxiety in a rat model of PTSD and decreased expression of IL-1β and TNF-α while increasing BDNF expression in the hippocampus[7]. This indicates that the effect of ibuprofen on PTSD was moderated by decreased anti-inflammatory activity and increased expression of BDNF in the brain.

Glucocorticoids are another class of drugs that can be employed to treat the symptoms of PTSD. Glucocorticoids work to suppress the inflammatory response following exposure to stress by promoting the production of anti-inflammatory cytokines and suppressing the production of pro-inflammatory cytokines. Clinical trials have shown that glucocorticoid treatment combined with psychotherapy can improve PTSD symptoms. Glucocorticoid administration after prolonged exposure, however, has been shown to not have significant effects on eliminating PTSD symptoms alone. Studies investigating the prophylactic effects of glucocorticoids following trauma exposure found that glucocorticoid treatment following an acute traumatic event was able to significantly reduce stress symptoms and the incidence of PTSD[7].

In addition to these approaches, angiotensin-converting enzyme inhibitors, noradrenergic beta-receptor blockers, angiotensin receptor blockers, and cannabinoids also have beneficial effects when used to treat PTSD. There are several mechanisms by which they do this through suppressing inflammation[7]. There is a growing body of strong evidence that supports

the use of immunotherapy to reduce PTSD symptoms, including inflammation. The drugs in this review are generally safe with proper oversight and are underutilized for PTSD. Given that glucocorticoids and noradrenergic beta-receptor blockers can work prophylactically to reduce the incidence of PTSD following a traumatic event, further research and applications are warranted for trauma-related conditions. If there is further evidence that glucocorticoids can work prophylactically, they can be a supplement to other treatments, such as stellate ganglion blocks, for individuals who arrive at the hospital after an intensely traumatic event, possibly blocking the development of PTSD. The link between PTSD, the brain, and inflammation produces the potential for anti-inflammatory treatment as a prophylactic intervention after an acute traumatic event, but before the onset of PTSD.

Discussion

This qualitative systematic review aims to highlight several novel therapies for PTSD as well as the limitations of their current studies. Some common limitations in novel research for PTSD include low adherence rates, funding/participant bias at military hospitals funded by the Department of Defense, and low generalizability rates given the limited demographics of study participants. These issues, in combination with a disorder that is not yet fully understood, greatly hinder widespread access to groundbreaking treatments for PTSD.

The identification of pressure-sensitive and oxygen-sensitive genes through hyperbaric oxygen therapy can possibly be used in combination with gene therapy to upregulate these genes. This could potentially be used to enhance the effects of hyperbaric oxygen therapy under normal atmospheric conditions. Hyperbaric oxygen therapy is commonly used to assist in neural regeneration after brain injuries or ischemic strokes, heal large wounds, and restore hearing after sudden deafness. HBOT exhibits several different mechanisms in which it has proven to be effective, but induced hyperoxia is ultimately the objective of the treatment. Forcing extra oxygen to perfuse throughout the body has many effects, and the oxygen works directly to

fight bacterial infections by releasing stem cells and various growth factors4. This in turn helps regulate the immune system and effectively reverse hippocampal tissue damage. Immune disorders are very commonly comorbid with PTSD, indicated by elevated levels of inflammatory markers in individuals with PTSD. These novel therapies have the potential to be administered in unison to maximize the effects of treatment[7].

Stellate ganglion blocks take an interesting approach to PTSD in that they utilize local anesthetic to block signal transmission to the brain. Stellate ganglion blocks are used for a wide variety of disorders, and the studies reviewed in this paper indicate that these injections can provide immediate relief to individuals with PTSD. These injections are safe when performed correctly, and more than one can be administered if one's symptoms return after an initial injection. Though there isn't relevant longitudinal research, it has shown to be safe to intermittently administer more anesthetic, indicating potential long-term relief with the use of several injections. The main side effect of SGBs, Horner's syndrome[16], is a temporary condition that causes minor neurological symptoms. Stellate ganglion blocks are low-risk treatments that are supported by several in vivo studies and clinical trials. The available data warrants their use as therapy for PTSD to provide immediate relief of physical, cognitive, and emotional symptoms.

Topiramate is another low-risk treatment that aims to reduce alcoholism in individuals with PTSD[8]. Topiramate is a widely accepted anticonvulsant that is now being used in other ways. Two clinical trials have yielded statistically significant results in different areas[9,22], indicating that topiramate can be an effective medication for alcohol use disorder comorbid with PTSD.

Some of these interventions have produced great results, assessed by a decrease in total symptom severity. Aside from stem cell therapy, these treatments are safe and effective for many individuals with PTSD and other disorders, and the qualitative evidence supports the mainstreaming of these therapies when administered in concert with psychotherapy.

Conclusion

With the limitations seen in the discussed studies, further in-depth investigation of all methods would increase the strength of statistical evidence, expand on PTSD-specific effects of each treatment, and generalize the outcomes to more diverse groups of patients. Offering different and more feasible approaches to these treatments would also popularize the effective treatment of PTSD symptoms according to their specific mechanism and significance in terms of the benefits, risks, and limitations they provide.

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