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Review

# Sympathetic system modulation to treat post-traumatic stress disorder (PTSD): A review of clinical evidence and neurobiology

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ABSTRACT

A review of clinical evidence and neurobiology on the effects of modulation of sympathetic system modulation to treat post-traumatic stress disorder (PTSD) is being presented . The review provides an overview of currently available treatments followed by efficacy of orally effective sympathetic blocking agents. The main focus of the review is the application of stellate ganglion blocks (SGBs) or a local anesthetic blockade of the sympathetic ganglion in the neck.

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## 1. Introduction

Post-traumatic stress disorder (PTSD) is a chronic anxiety disorder caused by seeing or experiencing traumatic events. The symptoms of PTSD include re-experiencing the event through flashbacks or nightmares, avoidance of stimuli which remind the victim of the traumatic event, and increased arousal, such as anxiety, anger or hypervigilance. A formal diagnosis of PTSD requires these symptoms to persist for at least a month and to cause significant disruption in one's personal and/or professional life. The person with PTSD has clinically significant distress and/or functional impairment.

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The potential for experiencing stress and trauma is a part of the human condition. Trauma may be physical or psychological, or both, and is caused by a variety of circumstances—domestic violence, terrorism, war. Its incidence is very likely to increase due to a multitude of factors. Military populations in particular are likely to be affected due to the ongoing, large-scale military operations in the past decade. The rise in international terrorism, combined with natural disasters such as tsunami, earthquakes, hurricanes and others, will likely exacerbate the increased prevalence of PTSD.

In addition to the psychiatric toll of PTSD, the financial burden of caring for civilian and military patients with this disorder is significant. In veteran populations affected by the Gulf Wars, financial impact is projected to be overwhelming–the eventual cost of covering lifetime benefits for veterans (medical, disability benefits, and social security) may reach $700 billion or more (Stiglitz and Bilmes, 2008). This is approximately the total overall cost of the first five years of war. The human cost of PTSD as well as financial are extreme, pointing to the pressing need for finding an effective, available treatment.

## 2. Historical perspective of PTSD

The earliest description of PTSD in the modern era was from the Civil War (1861–1865): "irritable heart" or "soldiers' heart" (Da Costa, 1871). According to a paper published in 1876 by Mendez DaCosta, MD, Civil War combat veterans with "soldiers' heart" had startle responses, hyper-vigilance, and heart arrhythmia, thus the first modern description of PTSD had a physiologic description. Further designations for PTSD followed. Current term PTSD was introduced in the 1980s in the United States and Western Europe. In DSM-III, multiple terms were applied to what is now called PTSD, many of which allude to a stress reaction and the biological effects on the heart, and presumably, the brain (American Psychiatric Association, 1980). The focus of this review is the biological approach to PTSD neurophysiology and biological treatments.

## 3. Current treatment approaches

### 3.1. Pharmaceuticals plus cognitive behavioral therapy (CBT)

Conventional PTSD treatment comprises two complementary strategies: (1) Medication to reduce anxiety and/or arousal (the selective serotonin reuptake inhibitors or SSRIs); (2) Cognitive behavioral therapy (CBT). Primarily indicated to address mood disorders, the SSRIs increase the amount of serotonin circulating in the brain but they have been shown to be helpful in mediating PTSD symptoms. However, side effects include sexual dysfunction (Balon, 2006), somnolence (Giner et al., 2005), and an increased risk for suicide (Giner et al., 2005). Four SSRIs have undergone clinical trials for efficacy in treating PTSD; these include citalopram (Celexa), fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft). Of these, only sertraline is currently FDA-approved with PTSD as an indication for use.

The CBT component of treatment helps the client change how he or she thinks about the traumatic event and the response to that event. Using exposure therapy, the client is reintroduced to portions of the traumatic event in a controlled, safe environment. The typical CBT course is three months with one to two visits per week. Alternatives with potentially similar efficacy include eye movement desensitization and reprocessing (EMDR). The dual nighttime symptoms of PTSD, nightmares and sleep disruption, are often unresponsive to medication (Raskind et al., 2006). While SSRIs are marginally effective for these symptoms among civilian populations (Brady et al., 2000), combat PTSD has been relatively impervious to pharmacological treatment (Zohar et al., 2002).

Other drugs are beginning to take position on the front lines in the battle against PTSD. Following the blood-thinner Plavix, Seroquel is the VA's second-biggest prescription drug expenditure each year since 2007; in the 2010 fiscal year, the agency spent $125.4 million on Seroquel, up from $14.4 million in 2001 (Scott, 2010). Similarly, the Department of Defense spending on Seroquel has increased nearly 700 percent since 2001, to $8.6 million last year, according to purchase records (Jones and Wessely, 2005). While FDA-approved for schizophrenia only, Seroquel is often used off-label for PTSD. However, the potential side effects, which include diabetes, weight gain and uncontrollable muscle spasms, have resulted in thousands of lawsuits. Researchers at Vanderbilt University published a study in the New England Journal of Medicine suggesting a new risk: sudden heart failure. The investigators found three cardiac deaths per year for every 1,000 patients taking anti-psychotic drugs like Seroquel (Schneeweiss and Avorn, 2009).

One of the most radical pharmaceutical treatments for PTSD is the street drug Ecstasy, or methylenedioxymethamphetamine (MDMA). In 2003, the National Institutes of Health (NIH) spent over $5 million to evaluate this approach, after which the FDA approved a clinical protocol to evaluate MDMA combined with talk therapy sessions. In the UK, one researcher believes a case can be made for MDMA-assisted psychotherapy, however he believed this drug should be used with "caution" (Sessa, 2007). Moreover, its relative lack of efficacy as well as its addictive nature has prevented its clinical use.

Considering the prevalence and intractable nature of the disorder, it is surprising that so little progress has been made in PTSD treatment using current approaches. In fact, an expert panel convened by the Institute of Medicine in 2007 found little evidence for the efficacy of most currently employed PTSD treatment modalities (Institute of Medicine October 17, 2007). The focus of this review is manipulation of the sympathetic nervous system to have a psychiatric effect, which the author believes is the new frontier for treating PTSD.

### 3.2. Sympathetic nervous system (SNS): its role in the development and maintenance of PTSD

The sympathetic nervous system (SNS) is part of the autonomic nervous system. Its role is to mobilize body's resources under stress, to induce the fight-or-flight response. It is also constantly active at a basal level in order to maintain homeostasis. In PTSD, the SNS is known to be chronically activated over the normal baseline levels (Lemieux and Coe 1995; Krystal et al., 1989). In large part, the activation of the SNS is accomplished by the increase of catecholamines, mainly epinephrine and norepinephrine. The role of norepinephrine in the brain is that of a neurotransmitter leading to arousal, selective attention, and vigilance which has been demonstrated in preclinical studies (Southwick et al., 1999). Specifically, elevated urinary norepinephrine has been identified among patients with PTSD (Mason et al., 1988). Similarly, norepinephrine concentrations in cerebrospinal fluid (CSF) are significantly higher in subjects with PTSD than among healthy controls and have been correlated with the severity of PTSD symptoms (Geracioti et al., 2001). Such notable increases in noradrenergic activity among subjects with PTSD suggest that reducing CNS noradrenergic activity could be effective, especially for arousal symptoms such as nightmares and startle reactions (Taylor et al., 2006). Orally active noradrenergic blocking or deactivating agents that have been used to moderate an over-active SNS include clonidine and prazosin, both were

original as antihypertesion medication. Both have been previously reported to have psychiatric effects on PTSD.

#### 3.2.1. Prazosin

A sympatholytic drug typically used to treat hypertension, Prazosin is in the class of alpha-adrenergic blockers which lower blood pressure by blocking the effects of norepinephrine, and in so doing relaxes the vessel walls. Interestingly, significant psychiatric effect was noted in double-blind placebo-controlled trials of Prazosin, which demonstrated a dramatic 70%–80% reduction in combat-related PTSD nightmares (Raskind et al., 2006). Although the evidence was less compelling, Prazosin also reduced PTSD-related anxiety during the day comparable to that observed with the SSRIs (Brady et al., 2000).

#### 3.2.2. Clonidine

Clonidine is an α2-adrenergic receptor agonist which suppresses the SNS outflow throughout the brain. Because clonidine activates the post-synaptic α2-adrenergic receptors in the central nervous system (CNS), it inhibits sympathetic activity (Ma et al., 2004). Contrary to the effects of Prazosin, Clonidine does not block the effects of norepinephrine directly but reduces the sympathetic activation in a central fashion in the brain.

A common clinical use of clonidine is the treatment of opioid withdrawal (Gowing et al., 2003; Kienbaum et al., 2003). Because acute opioid withdrawal elevates the startle response, which is blocked by Clonidine, it is thought that an adrenergic and anxiety component may be involved (Harris and Gewirtz 2004). The similarity between the startle response in opioid withdrawal and PTSD was observed more than two decades ago. It was thus suggested that Clonidine might be useful in treating PTSD (Kolb et al., 1984). Later, clonidine was employed specifically for the hyperarousal symptoms of PTSD (Sutherland and Davidson, 1994). While the SSRIs and other antidepressants often do not effectively treat the nightmares, hyperarousal, startle response, intrusive thoughts and agitation so characteristic of PTSD, Clonidine and Prazosin have demonstrated utility against these issues across a diverse population with PTSD.

The efficacy of Clonidine has been studied in animal models of stress-induced behavioral changes triggered by long-lasting locomotion reduction. In a double-blind placebo study, Clonidine was administered immediately after a single session of 8 min immobilization stress in a restraining box. When Clonidine was administered, locomotion reduction was not observed on any post-stress day. The results suggest that early intervention by noradrenergic inhibition might have a preventive effect on subsequent behavioral change (Shinba et al., 2001). In addition to these oral agents, it is now possible to directly affect the sympathetic nervous system with selective blocking techniques.

### 3.3. Psychiatric effects of cervical sympathetic system modulation

The stellate ganglion and upper thoracic ganglion (T-2) are the upper sympathetic ganglions that innervate the upper chest, the head and the brain. Many of the efferent sympathetic fibers from the thoracic ganglia (T-2) pass through the stellate ganglion (Uchida et al., 2002). Fig. 1 a connection from the stellate ganglion and the brain has been shown by the use of the pseudorabies virus injections (Westerhaus and Loewy, 2001). Pseudorabies virus allows identification of neural pathway connections one to three synapses away from the injection site. In this manner, the use of virus injection was used to identify cortical areas connected to the stellate ganglion, such as the amygdala (Fig. 1). This structure is known to be involved in the development of PTSD based on a functional MRI study (Liberzon and Martis, 2006).

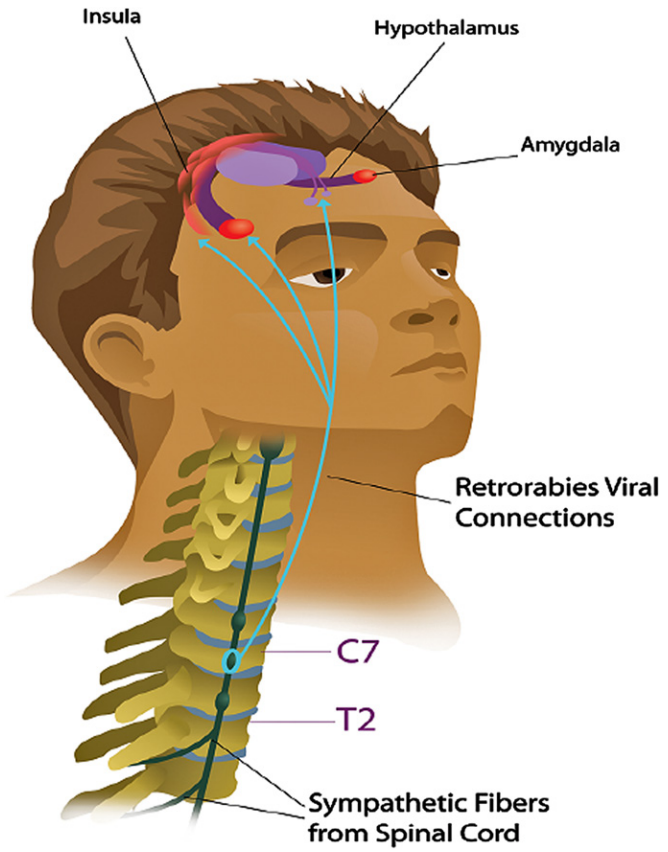


**Fig. 1.** Sympathetic fibers originate from the spinal cord at the thoracic level and enter the sympathetic chain leading to the brain. Thus, a T2 block is neurologically similar to a C6 or C7 block of the stellate ganglion.

### 3.4. Endoscopic sympathetic block (ESB) at the second thoracic vertebra (T2)

First pioneered in Finland by Dr. Telaranta, sympathetic system manipulation as a potential treatment for anxiety disorders is accomplished by clipping the sympathetic ganglia, via an endoscopic sympathetic block (ESB) at the second thoracic vertebra (T2). This procedure successfully treats severe anxiety and social phobias (Telaranta, 2003; Telaranta, 1998). When discussing this treatment advance, Teleranta noted the similarities in features between social phobias and PTSD—especially those caused by an overactive SNS, such as heart racing, hypervigilance, and avoidance of painful psychic situations (Telaranta, 2003). Primary author realized similarity of the stellate ganglion block (SGB) and ESB due to T-2 sympathetic nerve fibers passing thorough stellate ganglion and was able to predict the effect of SGB on PTSD.

### 3.5. Stellate ganglion block

The stellate ganglion block (SGB) is an anesthetic injection in a group of nerves in the neck, called the stellate ganglion. The procedure has been used to treat chronic pain since 1925 and recent pilot studies have demonstrated great promise as a successful intervention for PTSD, among other indications. The first documented use of SGB for psychiatric effect was its use in the resolution of depression by bilateral SGB as noted by clinicians at the Cleveland Clinic in 1947 (Karnosh and Gardner, 1947).

The first case study of successful use of the SGB to treat PTSD was reported by the author in 2008 (Lipov et al., 2008).

The patient was a civilian and victim of a violent crime who experienced an excellent response to SGB with marked resolution of PTSD symptoms. This was followed by a publication by Dr. Sean Mulvaney and his team at Walter Reed Army Medical Center, where a significant resolution of PTSD symptoms in two Operation Iraqi Freedom veterans was reported over one year (Mulvaney et al., 2010). Further report by the author demonstrated efficacy in 6 out of 8 patients treated and recently appeared in Military Medicine journal. A rat model was used to demonstrate efficacy of superior cervical sympathetic ganglion block (performed at C3 vs. C7, as in a traditional SGB in treating despair among rats (Park et al., 1997).

The SGB is performed by an anesthesiologist or pain medicine physician. The patient is administered a local anesthetic to numb the skin and surrounding tissue. A needle is then inserted next to a cervical vertebra 6 (C6), on the right side. (Because the traditional SGB is administered at C7, this innovation in technique at C6 is called the Chicago Block, where it was first described.) A dye is then injected to help target placement of the needle using X-ray guidance. When correct location is confirmed, a long acting local anesthetic is injected. The anesthetic blocks the sympathetic impulses sent by the ganglion to the brain. The Chicago Block appears to work only when administered on the right side, that being another reason for designation "Chicago Block" (Lipov et al., 2009). To date, 57 patients were treated in author's clinic and over 40 were treated in military installations, all for PTSD symptoms. {Private communications, unpublished data}. The results of Chicago Block have been very encouraging.

## 4. Discussion

### 4.1. Proposed mechanism of action for invasive SNS procedures

The best understood member of the neurotropic family, nerve growth factor (NGF) regulates a variety of signaling events such as cell differentiation and survival, growth cessation, and apoptosis (death) of neurons (Snider, 1994). The body responds to chronic stress by increasing NGF levels (Smith, 1996) and NGF is also known to be elevated immediately prior to soldiers' first parachute jump (Alleva et al., 1996) thus demonstrating a connection between NGF, stress and possibly PTSD. Further studies have demonstrated intracerebral NGF increase leading to retrograde transport of NGF from the intracerebral site to the stellate ganglion (Johnson et al., 1987). Next, NGF concentration increase at the stellate ganglion has been shown to lead to sprouting (new nerve growth) at the sympathetic end terminals which is NGF dependent (Chen et al., 2001), which, in turn, causes increased norepinephrine (NE) levels. This cascade has been seen in rat model, where infusion of NGF in the rat brain leads to an increase in NE (Isaacson and Billieu, 1996). More evidence points to NE being involved in PTSD where urine levels of NE are known to increase in PTSD (Kosten et al., 1987). Thus, it appears that trauma triggers a neurobiological cascade that ultimately leads to PTSD. We believe the reversal of this cascade occurs following application of a local anesthetic to the stellate ganglion. We believe this occurs due to the effect of local anesthetic application to the stellate ganglion nerve tissue leading to the reduction of NGF that is essential for maintenance of sprouting, since sprouting is NGF dependent(Takatori et al., 2006). This NGF decrease leads to the death of new nerve shoots (Gatzinsky et al., 2004).

The NGF model may also explain the phenomenon of "soldiers' heart" or "irritable heart" (Da Costa, 1871), today referred to as cardiac arrhythmia. We know that an increase of NGF levels in humans can lead to a cardiac QT prolongation and heart "irritability;" modulation of the QT interval is possible by cardiac sympathetic nerve sprouting as evidenced by a canine model of sudden cardiac death (Chen et al., 2001; Zhou et al., 2001).

## 5. Conclusion

In summary, the sympathetic nervous system appears to mediate PTSD. Encouraging reports have been published recently regarding improvements in PTSD symptoms following direct SNS modulation. The double-blind, placebo-controlled rat studies which demonstrate significant improvement in PTSD models speak to the efficacy of those approaches as do the early reports of use of SGB in humans for treatment of PTSD. It is our sincere hope that in the near future, invasive sympathetic modulating techniques (with or without polypharmacy and/or cognitive therapy) will significantly reduce the incidence of PTSD and its socio-economic sequelae. A number of studies are underway to quantify the efficacy of those approaches.

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**Conflict of interest**

There are no conflicts of interest.

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