Dual Sympathetic Block
DSB FOR ANXIETY

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Introduction

Anxiety is one of the most common psychiatric disorders in the United States (1). Generalized Anxiety Disorder (GAD) is a category of anxiety disorders in which excessive, persistent, and unrealistic fear, worry, and feeling of being overwhelmed is accompanied by nonspecific physiological symptoms (increased heart rate, shortness of breath, chest pain, hyperventilation, sweating, nausea, trembling), cognitive symptoms (fear of losing control, fear of physical injury, confusion), and behavioral symptoms (restlessness, pacing) (2-4). Since the onset of the COVID-19 Pandemic, the estimated global prevalence of anxiety disorders has substantially increased from 7% to 25% (5).

Although there are many contributing factors to the development of GAD, such as biopsychosocial and genetic factors, many cognitive, physiological, and behavioral symptoms associated with this disorder are hypothesized to be the consequence of overstimulation of the sympathetic nervous system (SNS) in response to perceived threat(s) (2-7). The SNS, a branch of the autonomic nervous system, coordinates with the central nervous system to process information about stress, impending danger, and fear into a physiological response. These functions are essential for survival as the SNS elicits various appropriate responses to stressful stimuli, such as liberating energy to equip the body to deal with emergent situations. As SNS signaling is primarily responsible for executing involuntary physiological responses to fear-inducing stimuli, SNS hypersensitivity is hypothesized to sustain and/or exacerbate symptoms of anxiety disorders, such as GAD (7-8).

Consequently, overstimulation or dysregulation of SNS signaling can lead to dysfunctional and inappropriate physiological responses (i.e. dysautonomia) (9). Dysautonomia is characterized by abnormal activity of involuntary body functions that are regulated by the SNS, such as heart rate, breathing, and digestion (8-10). Dysautonomia can have detrimental effects on various organ systems and can severely impair quality of life (10). GAD is associated with numerous physiological abnormalities that reflect a dysfunctional autonomic state, such as decreased vagally-mediated heart rate variability (HRV) (11-12). Reduced HRV is indicative of cardiac autonomic dysfunction (11, 13). As such, dysfunctional autonomic signaling may be involved in the maintenance and/or development of physiological abnormalities in GAD pathophysiology (9, 11-16).

Anxiety and PTSD Comorbidity

GAD and Post-Traumatic Stress Disorder (PTSD) are among the most common co-occurring mental health conditions, with at least an estimated 50% comorbidity rate in civilian populations and up to 68-91% in veterans (8, 17-18). The quadripartite model of psychopathology, a model widely used to explain comorbidity of psychiatric conditions,

proposes that psychiatric disorders are defined using two measurements, general distress and specificity (17). In accordance with this model, GAD and PTSD are thought to have high levels of general distress, the measurement which describes negative affect and externalizing symptoms, thus leading to high comorbidity (17). Additionally, evidence from a longitudinal clinical study of physical trauma survivors suggests that anxiety sensitivity predicts the severity of subsequent PTSD symptoms and severity of PTSD symptoms later predicts sensitivity to anxiety (19). The reciprocity between sensitivity to anxiety and severity of PTSD symptoms provides further evidence of a complex and highly interconnected relationship between anxiety and PTSD pathophysiology (19).

Among the shared neurobiological features between PTSD and GAD, hypersensitivity and hyperreactivity to stress are particularly relevant to the hypothesis supporting the potential of SGB in GAD symptom management. Research indicates there is a significant overlap of stress response and fear/anxiety response neurocircuitry, suggesting that these physiological response mechanisms that are atypical in PTSD and GAD are closely related on a cellular level (20). Similarly, as previously described, biomarkers of an exaggerated stress response are evidenced in both PTSD and GAD patients, further supporting the hypothesis of overlapping pathological abnormalities and mechanisms contributing to GAD and PTSD pathophysiology (11, 21).

Autonomic dysfunction may, at least in part, contribute to the development of similar characteristic manifestations of GAD and PTSD (e.g. impaired relaxation response, hyperarousal, irritability) (22) Although the comorbidity of PTSD and GAD is common, many patients who exhibit similar symptoms may not meet the strict DSM-V criteria for the diagnosis of either of these disorders. Autonomic dysfunction has been proposed as an explanation for the pathological mechanism that leads to these similar clinical presentations because patients with dysfunctional SNS responses exhibit many of the same symptoms as patients with PTSD and/or GAD (22). As such, developing management strategies that target autonomic dysfunction has the potential to have multiple therapeutic applications for mental health conditions.

Risk Factors for Anxiety

Due to the high prevalence of anxiety disorders in the general population and their associated rates of impairment and disability, identifying risk factors for anxiety disorders remains important for developing targeted prevention and treatment protocols. Risk factors for anxiety include familial history of Major Depressive Disorder (MDD), genetic and environmental liability, disturbed family environment, number of traumatic experiences endured, and low educational attainment (23). For example, adults who experienced childhood abuse are more susceptible to developing an anxiety disorder due to existing genetic polymorphisms, with genetic polymorphisms CRHR1 and CRHR2 being the most common (24). In addition, research has shown that carriers of the 5-HTTLPR short allele are susceptible for developing GAD (25). Ultimately, genes contribute 30-50% of the factors toward developing an anxiety disorder (Patriquin, 25). Such genetic vulnerability interacts with environmental factors (i.e. stress, trauma, etc.) that result in epigenetic mechanisms that produce clinically significant anxiety

symptoms as early as in utero stages of life (Patriquin 25). Epigenetic mechanisms include DNA methylation (results in repression of gene expression) and acetylation of chromatin structure (results in facilitation of gene expression), which ultimately influence behavioral phenotypes (24).

According to cohort studies involving general adult populations, other risk factors for developing anxiety disorders include high frequency of substance usage, including cigarette smoking, alcohol consumption, and cannabis usage (26). Bivariate analyses between MDD and GAD have demonstrated that both disorders have similar risk factors, explained by shared genetic and environmental liability (23). In addition to the large co-occurrence rate between GAD and PTSD, there are also large rates of comorbidity among GAD and MDD, that ranges from 40-98% according to treatment studies (23, 25). Further, numerous twin studies indicate high genetic correlations between MDD and GAD, suggesting that MDD and GAD are closely related (25). Due to evidence showing that GAD is often a precursor of MDD, it is necessary to effectively treat GAD and thus lower a patient's risk of developing MDD (25).

Anxiety Pathogenesis

General Anxiety Disorder (GAD) develops through long-term exposure to acute stressors, resulting in chronic maladaptive stress responses in reaction to threats (real or perceived). Acute stressors are sensory impulses or external stimuli that travel through nerve fibers in the periphery to the thalamus, the sensory relay station of the brain. Thalamic nuclei subsequently relay sensory signals to the cortex and the basolateral complex (BLA) of the amygdala, the center of processing fearful and threatening stimuli. Research has demonstrated increased activity in the amygdala in both GAD and MDD groups compared to healthy controls (25).

Upon processing of threatening stimuli, the central nucleus of the amygdala (CeA) outputs activation of the locus coeruleus (LC). The LC is made up of a large cluster of noradrenergic neurons that contribute to the body's anxiety responses such as rapid heartbeat, increased blood pressure, sweating, and pupil dilation. CeA also sends signals via corticotropin-releasing factor (CRF) neurons to the central and peripheral noradrenaline systems and to the paraventricular nucleus (PVN) and lateral hypothalamus (LH) of the hypothalamus. Upon stress exposure, the hypothalamus releases corticotropin-releasing factor (CRF), which regulates the hypothalamic-pituitary-adrenal (HPA) axis by initiating downstream events which culminate in the release of glucocorticoids, such as cortisol, from the adrenal cortex. Cortisol has been commonly referred to as the "stress hormone" and excessive activation of the HPA axis has been associated with the development of GAD (29).

The hypothalamus also activates the sympathetic nervous system, also known as the body's "fight or flight" response, by sending signals through the autonomic nerves to the adrenal glands. These glands then secrete the hormone epinephrine (adrenaline) into the bloodstream, eliciting characteristic anxiety-related physiological and behavioral responses, like defensive physiological reactions.

Meanwhile, the CeA also activates many midbrain regions and nuclei that mediate the fear response, including the periaqueductal gray (PAG), parabrachial nucleus (PBN), the caudal reticular pontine nucleus of the reticular formation (RPC), and the dorsal motor nucleus of the vagus (DMN). Stimulation of these various structures result in increased respiratory rate, increased heart rate and blood pressure, and in responses such as freezing, escape, and startle.

In addition, stress exposure is associated with activation of the prefrontal cortex, which is hypothesized to be responsible for modulating the body's fear response via continued interaction with the amygdala.

Current Anxiety Treatments

Conventional first-line PTSD treatment protocols include psychotherapy (i.e. "talk-therapy", prolonged exposure therapy, eye movement desensitization and reprocessing, and other evidence-based modalities) usually in combination with pharmacological interventions (30). Cognitive behavioral therapy (CBT) is typically regarded as the gold standard for psychotherapy treatment (31). Although this management approach may provide adequate symptom relief or even symptom remission in many patients, others continue to experience symptoms despite seeking care. The clinical benefits of psychotherapy may be limited in specific patient populations with certain psychosocial factors that may affect their response or comorbid personality or substance abuse disorders (31).

First-line pharmacological interventions include selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Other options include second-generation antidepressants, beta-blockers, steroids, antipsychotic drugs, mood stabilizers, and more (30). However, patients may have difficulty tolerating certain medications, especially those with an increased risk of associated adverse events (31). Adverse effects include potential fatal toxicity after overdose for antidepressants, possibility of worsening substance abuse with drugs like pregabalin, dependency, and withdrawal reactions after stopping treatment with an SSRI, benzodiazepine, pregabalin or paroxetine (31).

Daily exercise and increasing physical activity are also often a part of anxiety treatment protocols (31). Autogenic training, biofeedback and complementary medicine methods such as acupuncture, osteopathy, or homeopathy are also used as treatment options for anxiety disorders. However, clinical evidence supporting the efficacy of these treatments remains ill-defined (31).

As such, SGB may represent a novel therapeutic avenue for patients who struggle with GAD and do not respond to other therapies.

Dual Sympathetic Blockade for Anxiety

GAD is hypothesized to develop through chronic overstimulation of the sympathetic nervous system (SNS) in response to perceived threat(s) and dysfunctional autonomic signaling that contributes to physiological abnormalities (2-7, 9, 11-16). The stellate ganglion block (SGB) is an injection of local anesthetic that inhibits the sympathetic chronic stress response present in GAD by targeting the stellate ganglion, a sympathetic ganglion in the neck that produces sympathetic outflow to the head, neck, thorax, and upper extremities (31). Anesthetizing this region reduces classic anxiety symptoms such as increased heart rate, shortness of breath, chest pain, hyperventilation, sweating, nausea, trembling (31).

However, the exact mechanisms by which SGB relieves anxiety symptoms remains unknown. A proposed explanation for the efficacy of DSBs on reducing anxiety symptoms include the hypothesis that DSBs can decrease NGF levels in the stellate ganglion (31). A decrease in NGF reduces norepinephrine levels, thus inhibiting the hyper-aroused state of the sympathetic nervous system and reducing traditional anxiety symptoms.

Due to the significant comorbidity rate between GAD and PTSD and the surmounting evidence of the clinical benefits of SGBs on PTSD, it is highly indicative that SGBs may also alleviate GAD symptoms. For example, literature has revealed significant overlap between the neurocircuitry of the stress and anxiety responses involved in both PTSD and GAD pathogenesis (21). To support this claim, common biomarker profiles reflect a chronic stress response in both PTSD and GAD (11,21). Thus, autonomic dysfunction may underscore shared abnormalities in GAD and PTSD pathophysiology and suggest an explanation for the mechanism by which selective anesthetization of the C6 stellate ganglion may alleviate anxiety symptoms in GAD as well (11, 32).

Although the clinical data available on the effects of SGBs on GAD is limited, current research suggests that SGBs present as beneficial clinical treatment for patients with GAD with or without comorbid PTSD. For example, certain studies on the effects of SGBs on PTSD explore improvement in specific symptom clusters in a trans-diagnostic manner, showing that SGBs have shown to decrease hyperarousal and anxiety symptoms (31). A clinical case study (33) on 166 active duty service members investigated the effect of SGB treatment on symptoms associated with PTSD. Over 70% of the patients who received SGB had significantly improved scores on assessments of anxiety symptoms associated with PTSD which persisted beyond 3 to 6 months post-procedure, as measured by a mean reduction of 21.8 points in PCL-5 scores compared to baseline (33). Similarly, results from a multisite, blinded, sham-procedure, randomized clinical trial published in JAMA Psychiatry (29) reported a significant reduction in anxiety symptoms associated with PTSD following two SGBs at the C6 level, as measured by a

reduction in Generalized Anxiety Disorder 7-Item Scale scores following intervention. Thus, early clinical findings present promising, beneficial effects on SGBs on GAD symptoms.

Limitations

Despite these clinical findings on the effects of SGBs on PTSD-related anxiety symptoms, there are currently a lack of randomized trials examining SGB's effects on patients with GAD exclusively. For example, a systematic review on the efficacy of SGBs for various psychiatric disorders analyzed relevant research articles from 2016 onwards and concluded that efficacy findings can only be concluded on PTSD, with no relevant evidence identified for the clinical effects of SGB for anxiety (31). Another limitation is that the exact mechanism of action by which SGBs reduce anxiety symptoms remains unknown.

However, early clinical findings present promising results. Results from a recent case study on the efficacy of right-sided SGB in adjunct with pulsed radiofrequency suggests that self-reports of anxiety symptoms reduced by approximately 80-90% at 1-week post-procedure (31).

In addition, while the safety profile for SGB for PTSD patients has been well-studied, there is a lack of comprehensive review of the safety implications of SGB for GAD treatment. Thus, the need for further randomized clinical trials on the effects of SGB on anxiety symptoms still remains of utmost importance. Especially helpful are investigations on the appropriate SGB frequency and duration of symptom relief to justify the usage of SGB for GAD management.

Conclusion

Thus far, numerous case studies highlight the efficacy of SGB for PTSD and trauma-related anxiety. Further data on the effects of SGB on PTSD and trauma-related anxiety ought to be collected, in hopes of establishing future studies on SGB exclusively for GAD. Investigation into the long-term efficacy of SGBs and number of necessary SGB treatment sessions to achieve symptom relief may be warranted. This may be achieved through extended follow-up times, longer than 8 weeks, to examine the length of effect from an SGB injection.

More studies which explore the similarity of pathophysiology between GAD and PTSD may validate the hypothesis that these symptoms stem from autonomic dysfunction, and thus may be treated via SGB injections. Research ought to examine the exact mechanism of action of the SGBs in GAD and other psychiatric disorders.

Much of the research landscape on the effects of SGBs have emphasized diagnosis-specific effects. However, recently, treatments for psychiatric disorders have focused on improving specific symptom clusters, so SGB may be used to treat various psychiatric disorders, such as anxiety, schizophrenia, MDD, etc (31). For example, previous studies have reported certain positive clinical effects of SGB including improvement in avoidance, pain and physical functioning, memory, and sleep, that may reduce severity of symptoms across psychiatric disorders (31).

While further research on the efficacy of SGBs for GAD is warranted, SGBs thus far have shown to have significant potential benefit in various psychiatric disorders, especially for patients who have not responded to traditional, first-line treatment options. (31)

References

1. Munir S, Takov V. Generalized Anxiety Disorder. In: StatPearls. Treasure Island (FL): StatPearls Publishing; January 9, 2022.
2. Patriquin MA, Mathew SJ. The Neurobiological Mechanisms of Generalized Anxiety Disorder and Chronic Stress. Chronic Stress (Thousand Oaks). 2017;1:2470547017703993. doi:10.1177/2470547017703993
3. DeMartini J, Patel G, Fancher TL. Generalized Anxiety Disorder. Ann Intern Med. 2019;170(7):ITC49-ITC64. doi:10.7326/AITC201904020
4. Chand SP, Marwaha R. Anxiety. [Updated 2022 Feb 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470361/
5. Santabárbara J, Lasheras I, Lipnicki DM, et al. Prevalence of anxiety in the COVID-19 pandemic: An updated meta-analysis of community-based studies. Prog Neuropsychopharmacol Biol Psychiatry. 2021;109:110207. doi:10.1016/j.pnpbp.2020.110207
6. Chand SP, Marwaha R. Anxiety. [Updated 2022 Feb 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470361/
7. Wenner MM. Sympathetic activation in chronic anxiety: not just at the "height" of stress. Editorial Focus on "Relative burst amplitude of muscle sympathetic nerve activity is an indicator of altered sympathetic outflow in chronic anxiety". J Neurophysiol. 2018;120(1):7-8. doi:10.1152/jn.00220.2018
8. Roth WT, Doberenz S, Dietel A, et al. Sympathetic activation in broadly defined generalized anxiety disorder. J Psychiatr Res. 2008;42(3):205-212. doi:10.1016/j.jpsychires.2006.12.003
9. Alshak, Mark N. and Joe M Das. “Neuroanatomy, Sympathetic Nervous System.” StatPearls, StatPearls Publishing, 26 July 2021.
10. Goldstein, B. “Anatomy of the peripheral nervous system.” Physical medicine and rehabilitation clinics of North America vol. 12,2 (2001): 207-36.
11. Carnevali L, Mancini M, Koenig J, et al. Cortical morphometric predictors of autonomic dysfunction in generalized anxiety disorder. Auton Neurosci. 2019;217:41-48. doi:10.1016/j.autneu.2019.01.001
12. Dutt R, Shankar N, Srivastava S, Yadav A, Ahmed RS. Cardiac autonomic tone, plasma BDNF levels and paroxetine response in newly diagnosed patients of generalised anxiety

disorder. Int J Psychiatry Clin Pract. 2020;24(2):135-142. doi:10.1080/13651501.2020.1723642
13. Teed AR, Feinstein JS, Puhl M, et al. Association of Generalized Anxiety Disorder With Autonomic Hypersensitivity and Blunted Ventromedial Prefrontal Cortex Activity During Peripheral Adrenergic Stimulation: A Randomized Clinical Trial [published correction appears in doi: 10.1001/jamapsychiatry.2022.0434]. JAMA Psychiatry. 2022;79(4):323-332. doi:10.1001/jamapsychiatry.2021.4225
14. Lynch, James H et al. “Effect of Stellate Ganglion Block on Specific Symptom Clusters for Treatment of Post-Traumatic Stress Disorder.” Military medicine vol. 181,9 (2016): 1135-41. doi:10.7205/MILMED-D-15-00518
15. Ho TC, Pham HT, Miller JG, Kircanski K, Gotlib IH. Sympathetic nervous system dominance during stress recovery mediates associations between stress sensitivity and social anxiety symptoms in female adolescents. Dev Psychopathol. 2020;32(5):1914-1925. doi:10.1017/S0954579420001261
16. Fonkoue, Ida T et al. “Symptom severity impacts sympathetic dysregulation and inflammation in post-traumatic stress disorder (PTSD).” Brain, behavior, and immunity vol. 83 (2020): 260-269. doi:10.1016/j.bbi.2019.10.021
17. Price M, Legrand AC, Brier ZMF, Hébert-Dufresne L. The symptoms at the center: Examining the comorbidity of posttraumatic stress disorder, generalized anxiety disorder, and depression with network analysis. J Psychiatr Res. 2019;109:52-58. doi:10.1016/j.jpsychires.2018.11.016
18. Knowles KA, Sripada RK, Defever M, Rauch SAM. Comorbid mood and anxiety disorders and severity of posttraumatic stress disorder symptoms in treatment-seeking veterans. Psychol Trauma. 2019;11(4):451-458. doi:10.1037/tra0000383
19. Marshall GN, Miles JN, Stewart SH. Anxiety sensitivity and PTSD symptom severity are reciprocally related: evidence from a longitudinal study of physical trauma survivors. J Abnorm Psychol. 2010;119(1):143-150. doi:10.1037/a0018009
20. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology. 2010;35(1):169-191. doi:10.1038/npp.2009.83
21. Bremner JD, Krystal JH, Southwick SM, Charney DS. Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. Synapse. 1996;23(1):39-51. doi:10.1002/(SICI)1098-2396(199605)23:1<39::AID-SYN5>3.0.CO;2-I
22. Summers, Mary R, and Remington L Nevin. “Stellate Ganglion Block in the Treatment of Post-traumatic Stress Disorder: A Review of Historical and Recent Literature.” Pain practice : the official journal of World Institute of Pain vol. 17,4 (2017): 546-553. doi:10.1111/papr.12503
23. Blanco C, Rubio J, Wall M, Wang S, Jiu CJ, Kendler KS. Risk factors for anxiety disorders: common and specific effects in a national sample. Depress Anxiety. 2014;31(9):756-764. doi:10.1002/da.22247
24. Akiyoshi J. *Seishin Shinkeigaku Zasshi*. 2012;114(9):1063-1069.
25. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5832062/

26. Zimmermann M, Chong AK, Vechiu C, Papa A. Modifiable risk and protective factors for anxiety disorders among adults: A systematic review. *Psychiatry Res*. 2020;285:112705. doi:10.1016/j.psychres.2019.112705
27. Chand SP, Marwaha R. Anxiety . NCBI. https://www.ncbi.nlm.nih.gov/books/NBK470361/. Accessed August 17, 2022.
28. Steimer T. The biology of fear- and anxiety-related behaviors. Dialogues Clin Neurosci. 2002;4(3):231-249. doi:10.31887/DCNS.2002.4.3/tsteimer
29. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci. 2006;8(4):383-395. doi:10.31887/DCNS.2006.8.4/ssmith
30. Ehret M. Treatment of posttraumatic stress disorder: Focus on pharmacotherapy. Ment Health Clin. 2019;9(6):373-382. Published 2019 Nov 27. doi:10.9740/mhc.2019.11.373
31. Kerzner J, Liu H, Demchenko I, et al. Stellate Ganglion Block for Psychiatric Disorders: A Systematic Review of the Clinical Research Landscape. Chronic Stress (Thousand Oaks). 2021;5:24705470211055176. Published 2021 Dec 8. doi:10.1177/24705470211055176
32. Kulkarni, Kalpana R et al. “Efficacy of stellate ganglion block with an adjuvant ketamine for peripheral vascular disease of the upper limbs.” Indian journal of anaesthesia vol. 54,6 (2010): 546-51. doi:10.4103/0019-5049.72645
33. Mulvaney, Sean W et al. “Stellate ganglion block used to treat symptoms associated with combat-related post-traumatic stress disorder: a case series of 166 patients.” Military medicine vol. 179,10 (2014): 1133-40. doi:10.7205/MILMED-D-14-00151
34. Rae Olmsted KL, Bartoszek M, Mulvaney S, et al. Effect of Stellate Ganglion Block Treatment on Posttraumatic Stress Disorder Symptoms: A Randomized Clinical Trial [published correction appears in JAMA Psychiatry. 2020 Jan 2;:] [published correction appears in JAMA Psychiatry. 2020 Sep 1;77(9):982]. JAMA Psychiatry. 2020;77(2):130-138. doi:10.1001/jamapsychiatry.2019.3474