Stellate Ganglion Block for the Treatment of Posttraumatic Stress Disorder Symptoms: A New Treatment Option

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Disclaimer

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Poll Question #1 (select all that apply)

- What is your role in VA?
  - Student/trainee/fellow
  - Clinician
  - Researcher
  - Administrator/manager/policymaker
  - Other

Poll Question #2 (select one)

- In which substantive field is your expertise focused?
  - Psychiatry/psychology/behavioral health
  - TBI
  - Anesthesiology/pain medicine
  - Other

What Is PTSD?

PTSD is a symptom complex triggered by exposure to actual or threatened death, serious injury, or sexual violence (direct exposure, witnessing, learning a relative/close friend was exposed, or indirect exposure to aversive details of trauma)

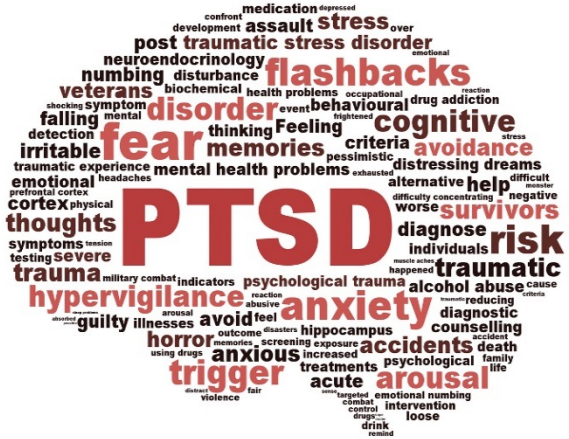
PTSD causes clinically significant distress or impairment of the individual's social interactions, capacity to work, or other important areas of functioning

PTSD is not the physiological result of another medical condition, medication, drugs, or alcohol

The duration of the disturbance is more than 1 month

Four categories of symptoms:

1. Intrusion
2. Avoidance
3. Negative alterations in cognitions and mood
4. Arousal



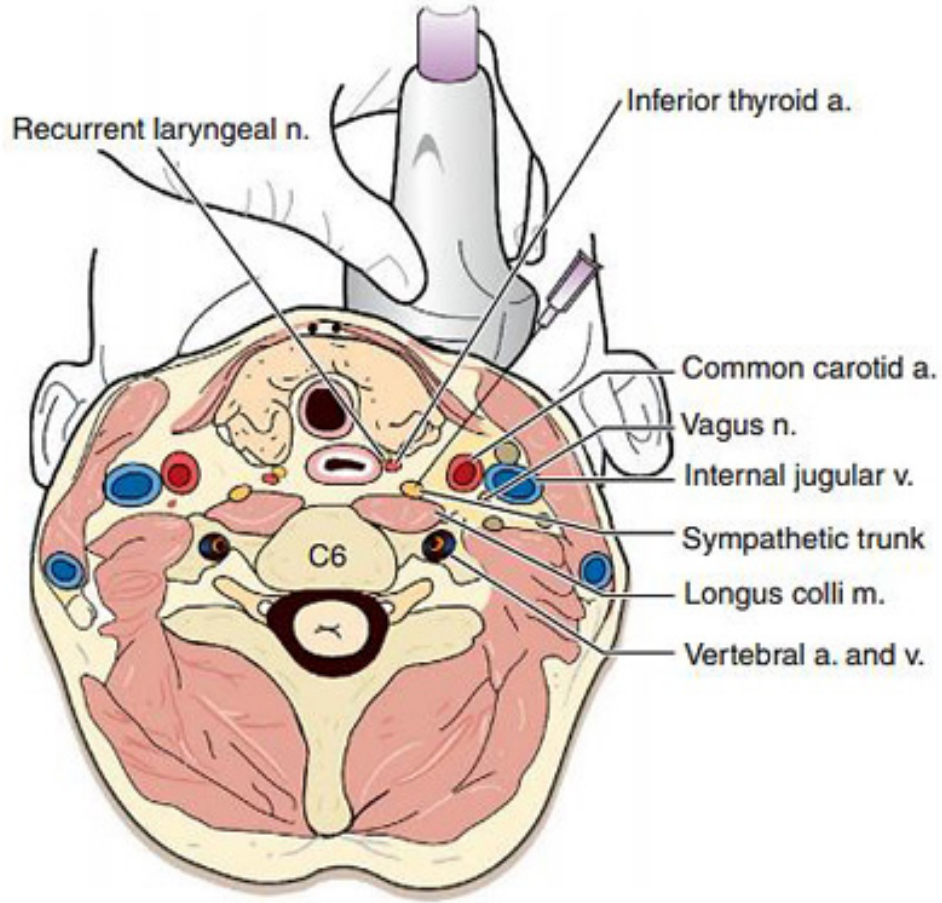
Current PTSD Treatments and Limitations

Psychotherapeutic and Pharmacologic

- 2017 National Center for PTSD (VA)
  - Exposure-based and cognitive processing/behavioral therapies
  - Select pharmacologic treatments (SSRIs, SNRIs), although smaller effect sizes
- Significant Disadvantages to Current Standard Treatments
  - Psychotherapy: significant delays in relief, possible deterioration of the patient
  - Pharmacotherapy: side effects and delays in symptom relief
  - Patient adherence issues

What Is the Stellate Ganglion?

- Stellate Ganglion
  - Cluster of nerves and nerve cells impacting the sympathetic nervous system
  - Located at the base of the neck near C6-C7
  - Major “switching station” for fight-or-flight response



Source: Bagherzadi.com

Poll Question #3 (select one)

- Which best describes your research experience?
  - Have not done research
  - Have collaborated on research
  - Have applied for research funding
  - Have led your own research
  - Other

Stellate Ganglion Block (SGB) for PTSD: A Brief History

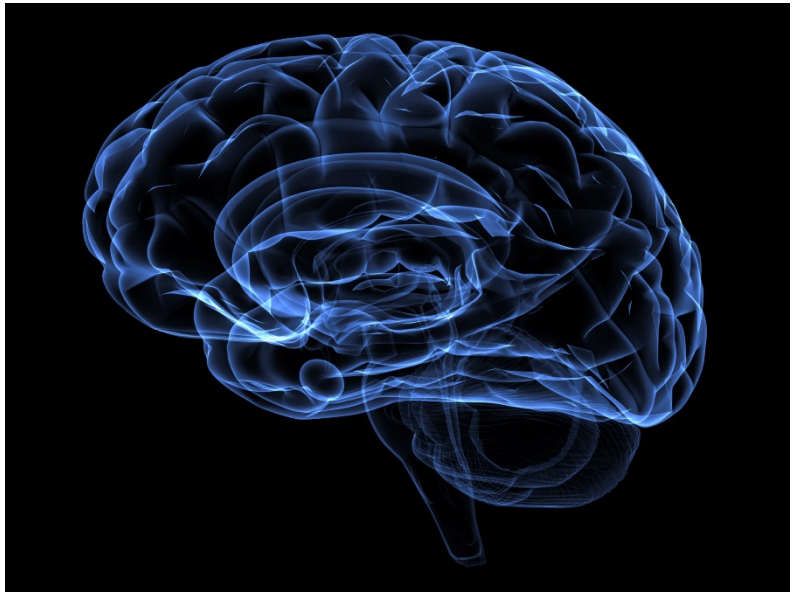
- 1990: Lebovits (Case Report)
  - Multiple gunshot wounds with resulting Chronic Regional Pain Syndrome and PTSD
    - Clinically significant PTSD symptom reduction
- 2008: Lipov et al. (Case Report)
  - Immediate symptom reduction between 80% and 90%
- 2015: Mulvaney et al. (Case Series; n=166)
  - More than 70% had clinically significant symptom reduction at 3–6 months
  - Those with more severe symptoms reported greater improvements
- 2016: Hanling et al. (RCT; n=42)
  - No significant difference between SGB and sham treatment
  - Methodological challenges
- 2016: Summers and Nevin (Literature Review)
  - "…evidence of substantial beneficial psychiatric effects…may reduce barriers to therapy, particularly among military populations."

Effectiveness and Patient Acceptability of SGB for PTSD Symptoms

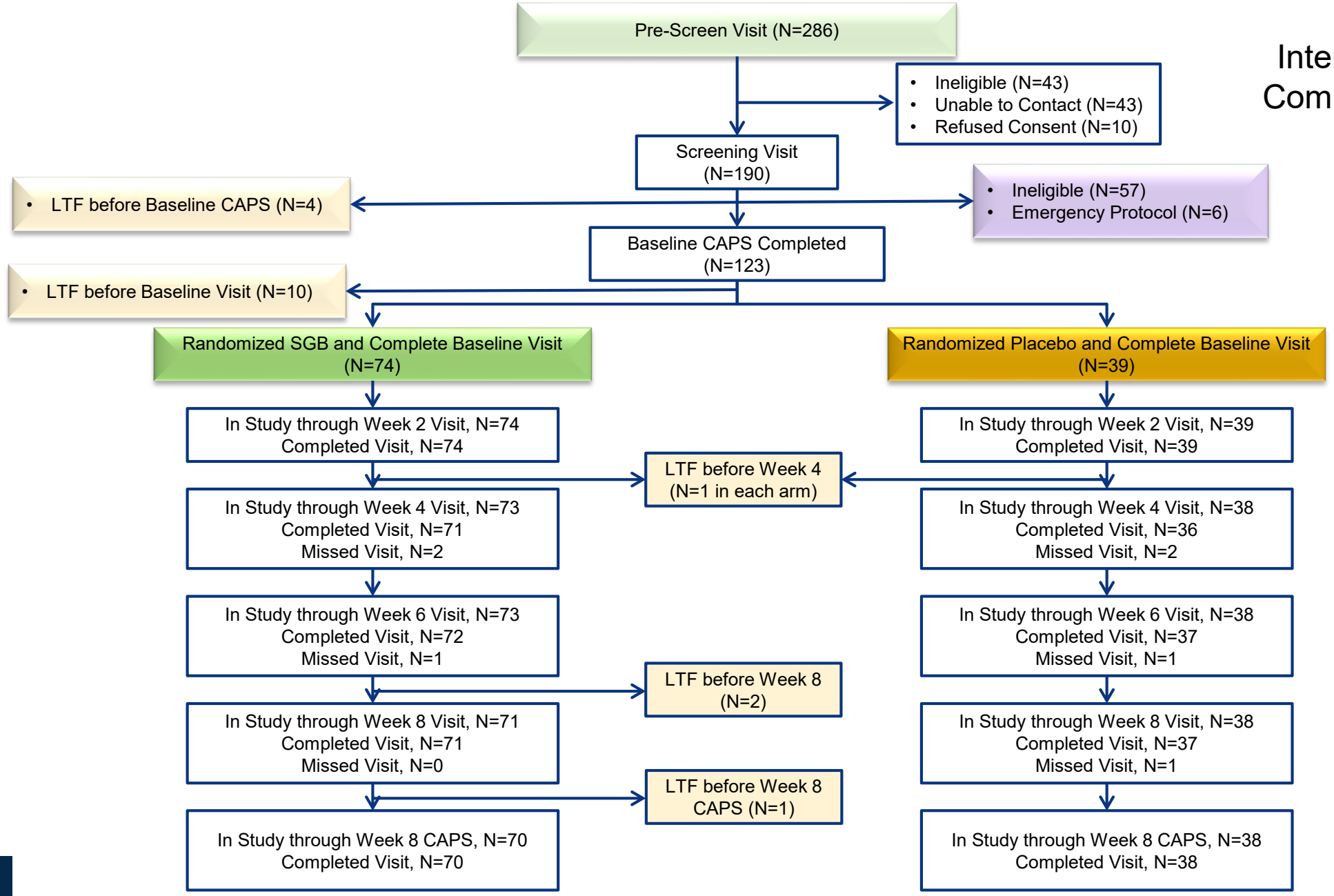
- First large-scale, multi-site study of SGB for PTSD
- Primary Research Questions
  - Does right-sided SGB performed at 0 and 2 weeks significantly reduce PTSD symptoms?
  - Does right-sided SGB result in significantly more improvement than sham?
- 3 Military Treatment Facilities (Womack Army Medical Center, Tripler Army Medical Center, Landstuhl Regional Medical Center)
- 2:1 active:sham randomization
  - 113 participants; 74 active, 39 sham
- Interventions at weeks 0 and 2
- CAPS-5 at baseline and 8 weeks
- Quantitative assessments at weeks 0, 2, 4, 6, and 8
- Qualitative assessment stratified by self-reported symptom change (better/the same or worse)

Inclusion/Exclusion Criteria

- Inclusion
  - Active duty status with anticipated stable assignment to installation
  - Stable dosing for at least 3 months if receiving psychotropic meds
  - Offered A-level treatment for PTSD symptoms prior to enrollment
  - PCL-C score of 32 or greater
- Exclusion
  - Prior SGB
  - History of bleeding disorder, glaucoma, schizophrenia, other psychotic disorder, bipolar disorder, or personality disorder (axis 2)
  - Allergy to anesthetics, pregnancy, current anticoagulant use, infection/mass at injection site, myocardial infarction within 6 months of procedure, hoarseness
  - Moderate/severe traumatic brain injury or substance use disorder
  - Suicidal Ideation during past 2 months
  - Undergoing Medical Board/Retirement
  - Any other condition deemed relevant by treating physician



Consort



Intention to Treat (ITT)
Completion Rate: 95.6%

Demographics

Baseline Characteristic	Treatment		P-Value
	SGB (N=74) N (%)	SHAM (N=39) N (%)	
Study Site[C]			
Womack	13 (17.6%)	9 (23.1%)	0.7769
Tripler	40 (54.1%)	20 (51.3%)	
Landstuhl	21 (28.4%)	10 (25.6%)	
Sex[C,1]			
Male	64 (86.5%)	36 (92.3%)	0.3565
Female	10 (13.5%)	3 (7.7%)	
Marriage Status[F,1]			
Married	67 (90.5%)	33 (84.6%)	0.3662
Neither married nor living as married	7 (9.5%)	6 (15.4%)	
Military Rank[F,1]			
Junior Enlisted	3 (4.1%)	3 (7.7%)	0.5559
Non-commissioned Officer	27 (36.5%)	11 (28.2%)	
Senior Enlisted	28 (37.8%)	19 (48.7%)	
Warrant Officer	5 (6.8%)	3 (7.7%)	
Commissioned Officer	11 (14.9%)	3 (7.7%)	
Age at Screening[T,1]			
Mean (SD)	37.4 (6.8)	37.0 (6.5)	0.7757
Min, Max	20, 50	25, 54	

C=Chi-square test; T=T-Test; F=Fisher Exact Test

[1]Collected at Screening Visit

Poll Question #4 (select one)

- How familiar are you with PTSD assessment?
  - Not at all familiar
  - Somewhat familiar
  - Very familiar

Baseline PTSD Scores

Outcome	SGB Mean (SD)	Sham Mean (SD)	P-Value
Baseline CAPS-5^{T}	37.61 (11.2)	39.82 (14.4)	0.37
Baseline PCL-5^{T}	41.54 (14.0)	43.23 (18.1)	0.58
Baseline PCL-C^{T}	53.30 (13.6)	54.95 (15.7)	0.56

T=T-Test

Unadjusted Means and Effect Size for Primary Outcome, by Treatment Group

Outcome Measure	Unadjusted Mean Score (Standard Deviation)		Effect[1], SD (95%CI)
	Sham (N=39)	SGB (N=74)	
CAPS-5 TSSS[2]			
Baseline[3]	39.82 (14.23)	37.61 (11.13)	
8-week follow-up[4]	33.68 (15.6)	25.67 (14.13)	
Mean change[4,5]	-5.79 (8.19)	-12.16 (12.86)	0.56, 0.09 (0.38, 0.73)

[1]Cohen's d effect size.
[2] Multiple imputation was performed for missing data on the primary outcome (5 participants did not complete the Week 8 CAPS).
[3] Adjusted for site.
[4] Adjusted for site and baseline CAPS TSSS.
[5] Adjusted mean reduction in TSSS from baseline to week 8 by treatment group from the per-protocol analysis and secondary analysis among those who fulfilled CAPS-5 diagnostic criteria for PTSD at baseline were consistent with those from the ITT analyses.

Individual decrease of 10 points in CAPS-5 score considered clinically significant (P. Schnurr, email communication, January 2017; F. Weathers, email communication, January 2017).

Unadjusted Means and Effect Size for Secondary Outcomes, by Treatment Group

Outcome Measure	Unadjusted Mean Score (Standard Deviation)		Effect[1], SD (95%CI)
	Sham (N=39)	SGB (N=74)	
PCL-5[6]			
Baseline	43.23 (18.13)	41.54 (14.03)	
8-week follow-up	38.11 (18.23)	29.49 (19.29)	
Mean change	-5.16 (13.99)	-12.63 (14.34)	0.53, 0.20 (0.14, 0.91)
PCL-C[6]			
Baseline	54.95 (15.67)	53.30 (13.64)	
8-week follow-up	50.65 (17.04)	42.41 (17.47)	
Mean change	-4.30 (14.17)	-11.45 (13.40)	0.52, 0.20 (0.14, 0.91)

[1]Cohen's d effect size.
[6] Adjusted for site, gender, age, visit, and interaction between visit and treatment.

Unadjusted Means and Effect Size for Secondary Outcomes, by Treatment Group (Cont'd)

Outcome Measure	Unadjusted Mean Score (Standard Deviation)		Effect[1], SD (95%CI)
	Sham (N=39)	SGB (N=74)	
PHQ-9[6]			
Baseline	12.69 (6.61)	12.57 (6.05)	
8-week follow-up	11.76 (6.25)	8.68 (6.02)	
Mean change	-0.92 (4.78)	-4.11 (5.55)	0.60, 0.20 (0.21, 0.99)
GAD-7[6]			
Baseline	12.49 (5.50)	12.39 (5.35)	
8-week follow-up	11.19 (6.38)	8.11 (6.02)	
Mean change	-1.22 (4.93)	-4.42 (5.80)	0.58, 0.20 (0.19, 0.97)

[1]Cohen's d effect size.
[6] Adjusted for site, gender, age, visit, and interaction between visit and treatment.

Unadjusted Means and Effect Size for Secondary Outcomes, by Treatment Group (Cont'd)

Outcome Measure	Unadjusted Mean Score (Standard Deviation)		Effect[1], SD (95%CI)
	Sham (N=39)	SGB (N=74)	
K6[6]			
Baseline	10.33 (6.01)	10.08 (5.55)	
8-week follow-up	10.00 (6.25)	7.80 (6.41)	
Mean change	-0.16 (4.59)	-2.52 (4.86)	0.49, 0.20 (0.11, 0.88)
Pain[6]			
Baseline	4.95 (2.21)	4.61 (2.40)	
8-week follow-up	4.86 (2.30)	4.10 (2.51)	
Mean change	-0.03 (1.44)	-0.56 (1.65)	0.34, 0.20 (-0.04, 0.72)

[1]Cohen's d effect size.
[6] Adjusted for site, gender, age, visit, and interaction between visit and treatment.

Unadjusted Means and Effect Size for Secondary Outcomes, by Treatment Group (Cont'd)

Outcome Measure	Mean Score (Standard Deviation)		Effect[1], SD (95%CI)
	Sham (N=39)	SGB (N=74)	
SF-12 Mental Functioning[6]			
Baseline	40.16 (9.84)	41.24 (11.32)	
8-week follow-up	40.17 (9.50)	42.83 (10.22)	
Mean change	-0.66 (7.21)	1.74 (7.58)	-0.32, 0.20 (-0.71, 0.06)
SF-12 Physical Functioning[6]			
Baseline	42.01 (7.87)	41.04 (8.16)	
8-week follow-up	41.28 (8.18)	43.43 (8.33)	
Mean change	-0.37 (7.02)	2.56 (8.15)	-0.38, 0.20 (-0.76, 0.01)

[1]Cohen's d effect size.
[6] Adjusted for site, gender, age, visit, and interaction between visit and treatment.

Adjusted Primary Outcome (CAPS-5 TSSS) for the SGB and Sham Treatment Groups, Per-Protocol and Baseline PTSD Populations

Outcome Measure	Per-Protocol Population [1]			Baseline PTSD Positive [2]		
	SGB (N = 59)	Sham (N = 29)	Difference; SE (95%CI)	SGB (N = 59)	Sham (N = 30)	Difference; SE (95%CI)
	Adjusted Mean Score (Standard Error)			Adjusted Mean Score (Standard Error)		
CAPS-5 TSSS						
Mean change	−12.41 (1.66)	−6.81 (2.23)	−5.59; 2.71 (−10.98, −0.21)	−13.86 (1.64)	−6.68 (2.19)	−7.18; 2.67 (−12.48, −1.87)

[1] The per-protocol population consists of those from the intent-to-treat (ITT) population but excludes participants who withdrew or were lost to follow-up prior to completion of the study, received a non-centrally randomized intervention, knew the intervening physician, completed visits outside of the prespecified window, or had a screening-to-baseline interval of more than 31 days.

[2] The Baseline PTSD Positive Population excludes participants who did not meet PTSD diagnosis criteria at the baseline visit, as defined by the CAPS-5.

Poll Question #5 (select one)

- How familiar are you with the concept of adverse events in research?
  - Not at all familiar
  - Somewhat familiar
  - Very familiar

Adverse Events

ID	Adverse Event	Assessment of Causality	Treatment Group
2054[a]	Temporary irritation of larynx which resulted in coughing	Possibly related	SGB
2054[b]	Pain and redness at injection site	Definitely related	SGB
2109[b]	Vasovagal syncope with insertion of the IV	Definitely unrelated	SGB
3008[a]	Detection of nodule or cyst (< 1 cm) in thyroid gland	Definitely unrelated	SGB
3028[a]	Self-resolving episode of bradycardia (30-second duration; minimum heart rate of 32)	Definitely related	SGB
3066[a]	Report of mild, relative increase in pre-existing right tinnitus	Definitely unrelated	Sham

[a] week 0 procedure.

[b] week 2 procedure.

Results Summary

Primary

- The mean improvement in CAPS-5 score 8 weeks post treatment among patients treated with SGB (-12.16 points) was significantly greater than the improvement in patients treated with sham (-5.79 points)
- The point estimate for mean improvement among participants receiving SGB exceeded the predefined clinically meaningful difference of 10 points for the CAPS-5 (-12.60 points, 95% CI -15.51 to -9.69)

Secondary

- Those receiving SGB had improved PTSD, depression, distress, anxiety, and pain symptoms, and physical and mental functioning, compared to those receiving the sham procedure.

** Of note, the proportions of participants by group who correctly guessed their treatment arm did not differ significantly from 0.5 (correct SGB 51.5%, sham 63.9%, p=0.23), which would be expected as a random guess of study arm (data not shown).*

Study Strengths and Limitations

Strengths

- Blinded, sham-procedure controlled randomized study
- Standardized, in-person training of providing physicians and research coordinators
- Greater than 90% power to detect 10-point difference between groups from week 0 to week 8
- Very high completion rate (5 participant lost to follow-up)
- Rigorous methods took into account lessons learned from previous studies
- Diverse study sites yet similar demographic distributions

Limitations

- Fewer participants enrolled than anticipated
- Unable to blind anesthesiologists to intervention they performed
- Potential participant unblinding from possible Horner's Syndrome

Qualitative Findings

SGB is acceptable to those who are suffering:

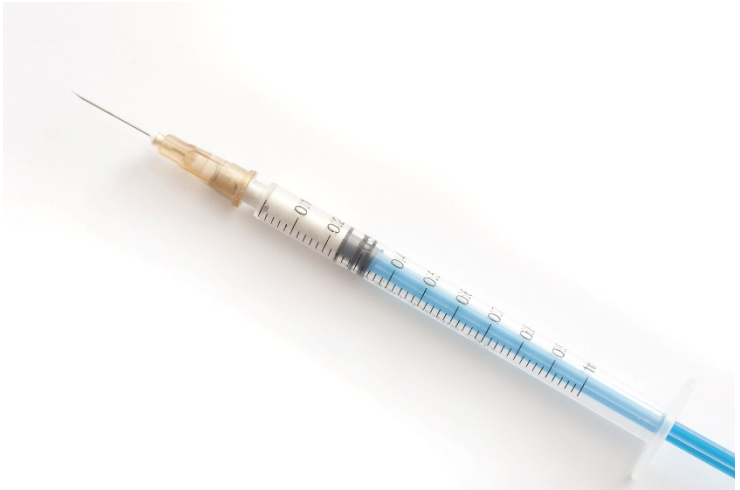
- “I would try anything that might help.”
- “I would rather die trying to get better than waiting around being miserable.”
- “At this point, if you told me that deploying again would fix my symptoms I would deploy again tomorrow.”

Physician engagement is critical:

- “The personal touch was important.”
- “Getting a call from the actual provider made me feel at ease.”

Family is a factor:

- “If it [SGB] helps me, it’ll help my family.”
- “My wife saying that I should try it [SGB] was the deciding factor.”
- Spouse: “He did this all on his own- I trust his judgment.”



Qualitative Findings (continued)

Reduction in hyperarousal:

- “I was more relaxed [after SGB]. It was what normal people feel like and I was missing out on that for a long time.”
- “It [SGB] gave me an extra second to not lose my cool.”
- “SGB gave me a buffer between the “0 to 10 zone.”

Ability to address things in psychotherapy:

- “[SGB] removed the negative physical aspects and allows you to think about mental health.”
- “SGB took away the internal anxiety so I could feel safe enough to process.”

Psychotherapy is important:

- “Basically, things just started coming out- it required a counselor.”
- “The racing thoughts were slowed but they were problematic because they stayed too long.” (From a service member who was not in psychotherapy)

Next Steps

RCT

- Evaluate the durability of SGB treatment- characterize treatment effect trajectory over the course of 8-week trial
- Evaluate whether DSM-5 Criterion E (marked alterations in arousal and reactivity) symptoms were more improved following SGB treatment than other Criteria
- Determine whether post-SGB Horner syndrome density moderated SGB treatment effect
- Determine the degree to which concurrent medication use is related to SGB effectiveness

Qualitative Study

- More thoroughly characterize participants' experiences with SGB
- Identify any gaps in pre-procedure information provision

More Information

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