QUERI

Evidence Brief: Effectiveness of Stellate Ganglion Block for Treatment of Posttraumatic Stress Disorder

Supplemental Materials

February 2017

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

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APPENDIX A: SEARCH STRATEGIES

Database: Ovid MEDLINE

(December 30, 2016)
Database: Ovid MEDLINE(R) <1946 to December Week 1 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 29, 2016>
Search Strategy:
---

1 stellate ganglion block.mp. (632)
2 (PTSD or post-traumatic stress disorder).mp. (22757)
3 Stress Disorders, Post-Traumatic/ (29126)
4 2 or 3 (35367)
5 1 and 4 (18)
6 remove duplicates from 5 (18)

Expanded Search

(February 7, 2017)
Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 4 2017>
Search Strategy:
---

1 (stellate adj5 block*).mp. (390)
2 nerve block.mp. or exp Nerve Block/ (12206)
3 exp Anesthetics, Local/ or anesthetics.mp. (73303)
4 bupivacaine.mp. (8470)
5 lidocaine.mp. (13981)
6 (nerve* adj5 block*).mp. (14395)
7 (sympathetic* adj5 block*).mp. (1491)
8 sympatholytic*.mp. (1941)
9 (local adj5 (anaesthetic* or anesthetic*)).mp. (26245)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (90120)
11 post traumatic stress disorder.mp. or exp Stress Disorders, Post-Traumatic/ (23908)
12 10 and 11 (81)
13 limit 12 to (english language and humans) (64)

Database: CINAHL

(December 30, 2016)
Database: CINAHL Plus with Full Text
Search Strategy:
---

1 “stellate ganglion block” (126)
2 PTSD OR post-traumatic stress disorder (7,224)
3 S1 AND S2 (12)

Expanded Search (February 7, 2017)

Database: CINAHL Plus with Full Text
Search Strategy:
---
1 nerve block (6,642)
2 local anesthetic* (1,861)
3 bupivacaine (3,328)
4 lidocaine (4,736)
5 nerve* N5 block* (6,968)
6 stellate adj5 block* (0)
7 sympathetic* N5 block* (297)
8 sympatholytic* (389)
9 local N5 (anaesthetic* or anesthetic*) (7,966)
10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (17,227)
11 PTSD (5,955)
12 post-traumatic stress disorder (2,813)
13 post traumatic stress disorder (2,813)
14 S11 OR S12 OR S13 (7,298)
15 S10 AND S14 (15)

Database: PsycINFO

(December 30, 2016)
Database: PsycINFO <1806 to December Week 4 2016>
Search Strategy:
---
1 stellate ganglion block.mp. (29)
2 (PTSD or post-traumatic stress disorder).mp. (30258)
3 exp Posttraumatic Stress Disorder/ (26439)
4 2 or 3 (34382)
5 1 and 4 (10)

Expanded Search (February 7, 2017)
Database: PsycINFO <1806 to January Week 5 2017>
Search Strategy:
---
1 (stellate adj5 block*).mp. (47)
2 nerve block.mp. or exp Nerve Block/ (245)
3 exp Anesthetics, Local/ or anesthetics.mp. (1491)
4 bupivacaine.mp. (219)
5 lidocaine.mp. (1020)
6 (nerve* adj5 block*).mp. (807)
7 (sympathetic* adj5 block*).mp. (198)
8 sympatholytic*.mp. (108)
9 (local adj5 (anaesthetic* or anesthetic*)).mp. (824)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (3800)
11 post traumatic stress disorder.mp. or exp Stress Disorders, Post-Traumatic/ (8323)
12 10 and 11 (12)
13 limit 12 to (human and english language) (12)

Database: Cochrane

(December 30, 2016)
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2016>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 21, 2016>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>
Search Strategy:
---
1 stellate ganglion block.mp. (124)
2 (PTSD or post-traumatic stress disorder).mp. (1960)
3 Stress Disorders, Post-Traumatic/ (1125)
4 2 or 3 (2245)
5 1 and 4 (1)

Expanded Search (February 7, 2017)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2016>
Search Strategy:
---
1 (stellate adj5 block*).mp. (135)
2 nerve block.mp. or exp Nerve Block/ (4639)
3 exp Anesthetics, Local/ or anesthetics.mp. (16210)
4 bupivacaine.mp. (8082)
5 lidocaine.mp. (7734)
6 (nerve* adj5 block*).mp. (5110)
7 (sympathetic* adj5 block*).mp. (467)
8 sympatholytic*.mp. (403)
9 (local adj5 (anaesthetic* or anesthetic*)).mp. (10088)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (26152)
11 post traumatic stress disorder.mp. or exp Stress Disorders, Post-Traumatic/ (1425)
12 10 and 11 (6)
13 limit 12 to english language (5)

Database: PILOTS

(December 30, 2016)
Search Strategy:
---
1 stellate ganglion block (16)

Expanded Search (February 8, 2017)

Search Strategy:
---
1 (stellate ganglion block) OR (stellate block OR nerve block) OR (anesthetics OR bupivacaine) OR (lidocaine OR sympathetic block) OR sympatholytic AND (post traumatic stress disorder OR PTSD) (98)

Systematic Review Searching

(December 5, 2016)
Database: Ovid MEDLINE(R) <1946 to November Week 4 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 02, 2016>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>
Search Strategy:
---

1 meta-analysis.pt. (81216)
2 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ (107793)
3 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. (111055)
4 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. (8042)
5 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. (18235)
6 (data synthes* or data extraction* or data abstraction*).ti,ab. (20009)
7 (handsearch* or hand search*).ti,ab. (8026)
8 meta-analysis.pt. (81216)
9 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ (107793)
10 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. (111055)
11 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. (8042)
12 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. (18235)
13 (data synthes* or data extraction* or data abstraction*).ti,ab. (20009)
14 (handsearch* or hand search*).ti,ab. (8026)
15 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. (20022)
16 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (197889)
17 (meta regression* or metaregression*).ti,ab. (5108)
18 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (197889)
19 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. (145258)
20 (cochrane or (health adj2 technology assessment) or evidence report).jw. (21091)
21 (meta-analysis or systematic review).ti,ab. (151446)
22 (comparative adj3 (efficacy or effectiveness)).ti,ab. (10226)
23 (outcomes research or relative effectiveness).ti,ab. (6709)
24 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab. (1498)
25 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (327917)
26 stellate ganglion block.mp. (632)
27 25 and 26 (7)
28 remove duplicates from 27 (7)
****

Grey Literature Searching

(December 22, 2016)

General Databases **Date Searched:** 12/22/2016	
Sources:	**Evidence:**
CADTH Grey Matters	https://www.cadth.ca/resources/finding-evidence/grey-matters Search: Stellate Ganglion Block Relevant results: None
Conference Papers Index	http://library.pdx.edu/dofd/subjects Search: Stellate Ganglion Block Relevant results: None
Grey Literature Report	http://www.greylit.org/home Search: Stellate Ganglion Block Relevant results: None
Clinical Trials	https://www.clinicaltrials.gov/ Search: Stellate Ganglion Block Relevant results: A Randomized, Placebo-Controlled Trial of Stellate Ganglion Block in the Treatment of Post Traumatic Stress Disorder NCT01629537 Status: Published, DOI: 10.1097/AAP.0000000000000402 The Efficacy of Stellate Ganglion Block as Post-traumatic Stress Disorder (PTSD) Therapy: A Pilot Study NCT01533610 Status: Unknown, the completion date has passed and the status has not been verified in more than two years
Clinical Trial Results	www.clinicaltrialresults.org/ Search: Stellate Ganglion Block Relevant results: None
WHO International Clinical Trials Registry Platform	http://apps.who.int/trialsearch/default.aspx Search: Stellate Ganglion Block Relevant results: No new results
RePORT Research Portfolio Online Reporting Tool	https://projectreporter.nih.gov/reporter.cfm Search: Stellate Ganglion Block Relevant results: None
OpenGrey Repository System for Information on Grey Literature in Europe	http://www.opengrey.eu/ Search: Stellate Ganglion Block Relevant results: None

Trip Turning Research Into Practice. Trip is a clinical search engine	https://www.tripdatabase.com/ Search: Stellate Ganglion Block AND PTSD Relevant results: No new results
UKCTG UK Clinical Trials Gateway	http://www.ukctg.nihr.ac.uk/default.aspx Search: Stellate Ganglion Block Relevant results: None
NICE National Institute for Health and Care Excellence	https://www.nice.org.uk/guidance?action=find Search: Stellate Ganglion Block Relevant results: None
Health Quality Ontario Publications and OHTAC Recommendations	http://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessments Search: Stellate Ganglion Block Relevant results: None
Scopus (limit to conference papers)	http://libguides.ohsu.edu/az.php?a=s Search: Stellate Ganglion Block Relevant results: None
DoPHER Database of promoting health effectiveness reviews	http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=53 http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9 Search: Stellate Ganglion Block Relevant results: None

APPENDIX B: LIST OF EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review, 9=Protocol for eligible study

#	Citation	Exclude reason
1	Alino J, Kosatka D, McLean B, Hirsch K. Efficacy of stellate ganglion block in the treatment of anxiety symptoms from combat-related post-traumatic stress disorder: a case series. Military Medicine. Apr 2013;178(4):e473-476.	E(6)
2	Alkire MT, Hollifield M, Khoshsar R, et al. Prolonged Relief of Chronic Extreme PTSD and Depression Symptoms in Veterans Following a Stellate Ganglion Block The Anesthesiology annual Meeting: Long Beach VA Healthcare System, Long Beach, California; 2014.	E(6)
3	Hickey AH, Navaie M, Stedje-Larsen ET, Lipov EG, McLay RN. Stellate ganglion block for the treatment of posttraumatic stress disorder. Psychiatric Annals. Feb 2013;43(2):87-92.	E(7)
4	Hicky A, Hanling S, Pevney E, Allen R, McLay RN. Stellate ganglion block for PTSD. The American Journal of Psychiatry. Jul 2012;169(7):760.	E(6)
5	Lipov E. The use of stellate ganglion block in the treatment of panic/anxiety symptoms (including suicidal ideation), with combat-related posttraumatic stress disorder. Posttraumatic stress disorder and related diseases in combat veterans. Cham, Switzerland: Springer International Publishing; Switzerland; 2015:179-196.	E(6)
6	Lipov E, Ritchie EC. A review of the use of stellate ganglion block in the treatment of PTSD. Current Psychiatry Reports. Aug 2015;17(8):599.	E(7)
7	Lipov EG, Joshi JR, Sanders S, Slavin KV. A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD). Medical Hypotheses. Jun 2009;72(6):657-661.	E(6)
8	Lipov EG, Navaie M, Brown PR, Hickey AH, Stedje-Larsen ET, McLay RN. Stellate ganglion block improves refractory post-traumatic stress disorder and associated memory dysfunction: A case report and systematic literature review. Military Medicine. Feb 2013;178(2):e260-e264.	E(6)
9	Lipov EG, Navaie M, Stedje-Larsen ET, et al. Local Anesthetics Offer First Biologic Treatment for PTSD. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2012;59(1):1-190.	E(6)
10	Lipov EG, Navaie M, Stedje-Larsen ET, et al. A novel application of stellate ganglion block: Preliminary observations for the treatment of post-traumatic stress disorder. Military Medicine. Feb 2012;177(2):125-127.	E(6)
11	Lynch JH, Mulvaney SW, Kim EH, de Leeuw JB, Schroeder MJ, Kane SF. Effect of Stellate Ganglion Block on Specific Symptom Clusters for Treatment of Post-Traumatic Stress Disorder. Military Medicine. Sep 2016;181(9):1135-1141.	E(6)
12	McLean B. Safety and Patient Acceptability of Stellate Ganglion Blockade as a Treatment Adjunct for Combat-Related Post-Traumatic Stress Disorder: A Quality Assurance Initiative. Cureus. 2015;7(9):e320.	E(6)
13	Mulvaney SW, Lynch JH, de Leeuw J, Schroeder M, Kane S. Neurocognitive Performance is Not Degraded After Stellate Ganglion Block Treatment for Post-Traumatic Stress Disorder: A Case Series. Military Medicine. May 2015;180(5):e601-604.	E(6)
14	Mulvaney SW, Lynch JH, Hickey MJ, 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. Oct 2014;179(10):1133-1140.	E(6)
15	Mulvaney SW, Lynch JH, Kotwal RS. Clinical Guidelines for Stellate Ganglion Block to Treat Anxiety Associated With Posttraumatic Stress Disorder. J Spec Oper Med. 2015;15(2):79-85.	E(7)

#	Citation	Exclude reason
16	Mulvaney SW, McLean B, de Leeuw J. The use of stellate ganglion block in the treatment of panic/anxiety symptoms with combat-related post-traumatic stress disorder; preliminary results of long-term follow-up: A case series. Pain Practice. Jul-Aug 2010;10(4):359-365.	E(6)
17	Navaie M, Keefe MS, Hickey AH, McLay RN, Ritchie EC, Abdi S. Use of stellate ganglion block for refractory post-traumatic stress disorder: a review of published cases. Journal of Anesthesia & Clinical Research. 2014;2014.	E(8)
18	Summers MR, Nevin RL. 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. Oct 14 2016.	E(8)

APPENDIX C: EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED STUDIES

Data Abstraction: Study Characteristics and Results

Author Year Study Design N	Age Sex Race	Military Status	Mental Health Treatment SUD	Baseline PTSD (CAPS, PCL)	Mean Change PTSD (CAPS, PCL) Int. vs Ctrl.	Baseline Depression* Anxiety** Pain***	Mean Change Depression* Anxiety** Pain*** Int. vs Ctrl.	Injection Site, Number of Injections
Hanling 2016[1] RCT 42	NR 81% Male White 61.9% Hispanic 19.0% AA 11.9% API 2.4% Did not answer 4.8%	Active duty 88.1% Retired 11.9%	Since deployment 9.5% During deployment 26.2% After deployment 69% SUD: NR	CAPS 86.76 PCL 65.90	CAPS 6.55 vs 8.76 PCL 1.96 vs 2.43	PHQ-9 18.77 BAI 29.33 VAS 47.34	PHQ-9 1.07 vs 1.45 BAI 1.70 vs -1.68 VAS -1.25 vs -1.78	C5 or C6 13 (31%) received one injection 29 (69%) received two injections

Abbreviations: NR = not reported; AA= African American; API= Asian/Pacific Islander; SUD = substance use disorder; Int. = intervention; Crtl. = control; CAPS = Clinician-Administered PTSD Scale; PCL = PTSD Checklist; PHQ-9 = *Patient Health Questionare-9; **BAI = Beck Anxiety Intervention; ***VAS = Visual Analog Scale

QUALITY ASSESSMENT OF INCLUDED STUDIES

Quality Assessment of RCTs

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider/ Patient masked?	Intention-to-treat (ITT) analysis?	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating (Good, Fair, Poor)
Hanling, 2016[1]	Unclear	Unclear	Unclear	Yes	No	Yes	Unclear	No	Fair
USA	No description of sequence generation	No information on allocation concealment	More active duty in SGB group (96.3% vs. 73.3%, P=0.05), and most were undergoing medical disability evaluation board, introducing potential for secondary gain		Yes		No information about adherence	47% overall, and differential (67% SGB vs. 40% control)	

Abbreviations: SGB = stellate ganglion block

STRENGTH OF EVIDENCE FOR INCLUDED STUDIES

Strength of Evidence per Intervention

SOE Grade	Study, Design (N)	Study Limitations*	Directness	Consistency	Precision**	Findings
Insufficient	Hanling 2016[1] RCT (42)	Medium	Indirect	Unknown	Imprecise	Results indicate insignificant decreases in PTSD scores in both groups, and no statistical differences between groups.

*High, medium, low based on study quality
**Precision based on confidence intervals for PTSD score (CAPS)
Abbreviations: CAPS= Clinician-Administered PTSD Scale

APPENDIX D: ONGOING STUDIES

Ongoing Studies

Investigator Title	Study design N	Study Sites	Treatment Comparator	Outcome	Status Expected Competition	Source Funding
Walters, Bradford Effectiveness and Patient Acceptability of Stellate Ganglion Block (SGB) for Treatment of Posttraumatic Stress Disorder (PTSD) Symptoms among Active Duty Military Members	RCT N= 240	Womack Army Medical Center, Fort Bragg, North Carolina Tripler Army Medical Center, Honolulu, Hawaii Landstuhl Regional Medical Center, Landstuhl, Germany	Stellate ganglion block (C6 or C7) at 0 and 2 weeks Sham injection (C6 or C7) at 0 and 2 weeks	CAPS-5 PCL-5 PHQ-9 GAD-7 VAS	Active, recruiting November, 2017	https://sgbstudy.rti.org/ United States Army Medical Research Acquisition Activity (USAMRAA) W81XWH-15-2-0015

Abbreviations: CAPS-5= Clinician-Administered PTSD Scale-5; PCL-5= PTSD checklist-5; PHQ-9= Patient Health Questionnaire-9; GAD-7= Generalized Anxiety Disorder-7; SF-12= 12-item short form survey; VAS= visual analog pain scale

APPENDIX E: PEER REVIEW

Comment #	Reviewer #	Comment	*Author Response*
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	None
2	2	Yes	None
3	3	Yes	None
4	4	Yes	None
5	5	Yes	None
Is there any indication of bias in our synthesis of the evidence?			
6	1	No	None
7	2	No	None
8	3	No	None
9	4	No	None
10	5	No	None
Are there any published or unpublished studies that we may have overlooked?			
11	1	No	None
12	2	No	None
13	3	Alkire, Michael T., et al . "Neuroimaging suggests that stellate ganglion block improves post-traumatic stress disorder (PTSD) through an amygdala mediated mechanism." American Society of Anesthesiology annual meeting. 2015., this is a VA study using PET scan in SGB Pts, 7 veterans treated	Added to Background as reference for discussion of amygdala mechanism.
14	3	Alkire, Michael T., et al . "Prolonged relief of chronic extreme PTSD and depression symptoms in veterans following a stellate ganglion block." American Society of Anesthesiology, October 11 (2014). 12 veterans treated with extreme PTSD	Added to Benefits section to highlight effects in extreme PTSD.
15	3	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 (2016). John Hopkins	We have already cited Dr. Summers' review in the Discussion, along with other prior reviews, to confirm that we agree with the conclusions of previous reviews that further research is needed to more precisely determine the balance of benefits and harms of SGB for PTSD.
16	3	Lynch, James H., et al . "Effect of Stellate Ganglion Block on Specific Symptom Clusters for Treatment of Post-Traumatic Stress Disorder." Military Medicine 181.9 (2016): 1135-1141. Specific symptoms affected by SGB in PTSD	Added to "Who is Most Likely to Benefit" section as supporting generation of the hypothesis that people with predominantly hyperarousal and avoidance types of symptoms may be more likely to benefit from SGB
17	3	McLean, Brian . "Safety and patient acceptability of stellate ganglion blockade as a treatment adjunct for combat-related post-traumatic stress disorder: a quality assurance initiative." Cureus 7.9 (2015). Safety and tolerance of SGB for PTSD	Added to Harms section

18	3	Navaie, M., et al. "Use of stellate ganglion block for refractory post-traumatic stress disorder: a review of published cases." J Anesth Clin Res 5.403 (2014): 2. review of literature to that date , 8 veterans with specific treatments summarized	This study was captured in our search and discussed in our report in multiple places as a source for our summary of frequently cited case series findings(ref 39).
19	3	Jeong, Seunghyun, et al. "The effects of stellate ganglion block on the electroencephalogram in rats." Journal of anesthesia 28.4 (2014): 601-605.	Added to Background as reference for potential sedative effects
20	3	Mechanism paper Lipov, Eugene G., et al. "A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD)." Medical hypotheses 72.6 (2009): 657-661.	Added to Background as reference for proposed prolonged effect
21	3	Hoge, Charles W. "Interventions for war-related posttraumatic stress disorder: Meeting veterans where they are." JAMA 306.5 (2011): 549-551.	Already included in Introduction as source for information on challenges of conventional therapy.
22	4	No	None
23	5	No	None
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
24	1	With regards the search strategy, there are extensive search terms for identifying evidence from specific methodological sources but the search terms to capture the intervention, condition or outcomes are very limited indeed. While I think it is highly likely there is only the one trial identified here there may be a case for some sensitivity scoping using alternative terms.	Per the 2016 O'Connell Cochrane review on local anaesthetic sympathetic blockade for complex regional pain syndrome, we added 9 new terms to capture the intervention. This resulted in 130 new citations, none of which met our inclusion criteria.
25	1	With regards interpretation, while remission or "responder" analysis was not presented, there is very little hint in the between group difference that the inclusion of those outcomes would have altered the outcome of the trial. It seems unlikely that with such trivial differences between groups that there is an important subgroup of "responders". Given that there is a case for clearly stating in the summary and conclusions that while it is possible that some patients benefit it is also possible that the technique is, in actuality, ineffective. This might also be better reflected in statements such as "evidence is insufficient to determine which veterans IF ANY are most likely to benefit…."	From the Executive Summary, we removed our criticism that the RCT lacked response rate assessment as we agree that this is less relevant under the circumstances of low and similar mean changes between SGB and placebo. Also, changed conclusion from "Findings from the first RCT of SGB for PTSD failed to confirm.." to "…were inconclusive, neither confirming nor refuting findings of rapid and high rates of clinically relevant improvement and low risk of serious adverse events from unblinded, uncontrolled case series
26	4	In general I greatly enjoyed the ESP report. I though the writing style struck a nice balance between being academic and digestible. I liked the organization of the report for the post part, however, I did find myself wishing the description of the RCT was formatted in a similar style to a published original research article (ie subjects, method, design, results) rather than a narrative paragraph.	For these Evidence Briefs, we have made a purposeful effort to assist readers with prioritizing information by front-loading our summaries with the main findings and most important details first, followed by other general information about subjects, methods and design.

27	4	In retrospect, I wish we'd made sure that a summary of the case series research was included in the list of study designs the report included. Since the majoring of the clinical benefit information would be have published in this format, I would feel more confident that we are truly aware of the reported clinical benefit for SGB if we included these publications. I looked at the original SOW and see that ESP did not initially include case studies in the review design, so that is likely a shortcoming on our part. Thankfully, we do have the list of articles that were not included due to ineligible study design, so we can look at the publications on our own. I feel that one of the great features of the report is the concise summary of findings, limitations, and especially the recommendations for addressing the limitations in future research. This last feature will be very helpful for our advisory council and is extremely valuable feedback for the submitter.	We added a brief summary of the case series studies to the results.
28	4	The authors were clear in their search strategy and summarized their findings and limitation of the RCT; however, I agree that a short summary of the actual RCT, since there was only one, would have been helpful to the reader. Otherwise, I do think that the paper provides a good overview of the limitations of evidence for SGB.	A summary of the RCT is located on page 9 under the heading "Randomized Trials"
29	2	Page 3, line 23: PTSD is no longer considered an anxiety disorder but is in a DSM-5 class of its own, trauma and stress-related disorders.	Changed to "…PTSD is a trauma and stress-related disorder…"
30	2	Page 4, lines 45-48: There is some skepticism about the proposed neuroanatomic connections and neurophysiological likelihood of important functional connections. Regarding input from the stellate ganglion to key brain regions such as dACC, amygdala, etc, there should be more discussion regarding the plausibility of this rationale for SGB's proposed efficacy for PTSD (e.g. that SGB actually does reduce amygdala activation. As for dACC, one would expect that more (not less) activation would be therapeutic for PTSD.)	As the mechanisms are speculative and are covered elsewhere, we are minimizing our discussions of the plausibility of the rationale.

31	3	Page 4 , line 44 : Biological rationale is not understood (agree) , references 41 discusses over activation of the amygdala(this is consistent with Dr Alkire demonstrated amygdal deactivation in PTSD patients following SGB) , however this does not explain a prolonged effect of SGB , Dr Lipov believes it is due to reduction of neurotropic factor NGF leading to loss of trauma induced sympathetic sprouting (lipov 2009)	Added Lipov 2009 and the following to the Background to describe proposed explanation for prolonged effect: *"The specific mechanism of action by which SGB may mitigate PTSD symptoms remains incompletely understood. SGB results in peripheral vasodilation, but the mechanism by which SGB impacts symptoms of PTSD is likely more complex. A proposed explanation for the prolonged effective of SGB on PTSD, as well as symptoms of hot flashes and complex regional pain syndrome, is that application of local anesthetic to the stellate ganglion leads to a reduction in nerve growth factor and a resulting decrease in sympathetic nerve sprouting and brain norepinephrine levels.{Lipov 2009}"*
32	4	The paper was definitely written for an audience with a clinical background. While I understand that it was aimed to be shared with SME's (p. 3, line 15), it was written for individuals with a high working knowledge of neurophysiology (e.g. p. 4, lines 46-49), which I believe does the paper a disservice and limits dissemination. I believe that including introductory information about why the stellate ganglion would be blocked near p.4, line 35; e.g. what does the stellate ganglion do, why is it activated in PTSD, and/or why would someone hypothesize that blocking the stellate ganglion would alleviate PTSD sx's would strengthen the rationale for the paper and intervention and allow for dissemination to a wider audience.	We added more introductory information as requested.
33	4	Additionally, while I'm not sure if it's relevant to the request, I'd suggest that the authors review the paper for grammar and sentence structure before completing the final draft, as there may be other edits besides the ones I have identified below. There were also places where edits could be made to cut unnecessary information (p. 4, lines 13-15, core components of the first-line psychotherapies) or where sentences, when read aloud, were awkwardly stated (p.3, lines 56-58, "regardless of the relationship to a PTSD diagnosis").	We kept the core components of first-line psychotherapies, but improved the grammar of p.3, lines 56-58 and others this reviewer identified.
34	4	p. 6, lines3-12: There are too many semi-colons in this sentence and no period at the end of it. I would suggest creating a new sentence on line 4, at "Although no definitive…"	Changed as suggested.

35	3	Page 9 , 34 to 37 , Dr Hanling reported utilizing" Lidocaine 1% was injected to the skin overlying the right C5 or C6 vertebra (level chosen on safest needle path based on individual patient anatomy)", the target for the SGB is C6 or C7 , while all placebo injections were performed at C6, NOT C5 , in fact no ganglion is described at C5 level . Thus with C5 placement and reduced amount of local anesthetic as discussed else where it is unclear as to the actual trial of the SGB (ref 57 in current report)	Added: Also, it is unclear whether the ropivacaine injection actually reached the stellate ganglion in all patients. Although the stellate ganglion is typically located at C6 to C7, the level of target needle placement was C5 to C6 in this study. Although the study author confirmed that the injection was “typically” at C6, some could have been at C5 and missed the stellate ganglion.
36	3	Page 9 , 34 to 37 . The concept of placebo with saline is problematic if not impossible with sympathetic injections , due to the inability to have an actual active placebo . I would suggest next study to have functional MRI as prior to and after the SGB for the end point plus CAPS .	Added to Implications: If a future RCT is undertaken, we suggest considering adding functional magnetic resonance imaging (fMRI) assessment both to improve our understanding of SGB’s neural mechanisms and to help elucidate the impact of inadequate blinding. Differences in fMRI results between SGB and control group participants could help refute an argument that clinical differences were due to knowing whether or not they got SGB.
37	3	Page 9 line 40 to 50 , Dr Hanling reported the patients that received 2 SGB's had a reduction of 19.8182 , well with in >15 point reduction in CAPS for demonstrated efficacy , vs single SGB 8.1538, and Sham 10.3846, Dr Hanling reported that " When looking at all participants (n = 29) who received 2 SGB treatments, paired t tests showed that the change in CAPS after the second treatment was greater than the change after the first treatment (P < 0.05)."	No change. The data in our Table 1 (page 9, line 40 to 50) are from Table 2 in Hanling 2016 for results BEFORE the crossover. The larger mean changes this reviewer is citing are understandably larger as they are from AFTER the crossover (Table 3 in Hanling 2016) in the subset of patient who initially got placebo and then SGB. We agree that in general improvements are greater after the second treatment and had already made this point on page 9, lines 7-9.
38	2	Page 9, lines 25-26 A 10 point reduction on the CAPS is generally considered the low end of clinical significance.	Changed to “≥ 10-15-point reduction on the CAPS”
39	2	Page 10, lines 41-46 Please provide the complication rate as you have done in the preceding paragraph.	Added that adverse event rates ranged from 0% to 14.3%
40	2	Pages 9-10 Some mention of relative costs should be inserted here.	Since we did not formally evaluate cost, we did not add them to our results section on pages 9-10. But we did add the following information about cost considerations to the Discussion: Cost of these innovative treatments compared to conventional psychotherapies and pharmacotherapies should also be assessed in the prioritization process. SGB costs have been estimated to be lower than conventional PTSD ($2,000 for two SGB injections vs a range of $6,000 to $30,000).[Lipov 2012] But, we have not formally evaluated comparative costs or how these estimates apply to the current VA environment.

41	3	Page 9 , 55 Safety of SGB for PTSD was assessed in over 100 patients by McLean (McLean)	At N=250, McLean 2015 is still too small to detect the types of significant complications that occurred in only 1.7 per 1000 patients in the 1992 German survey of 45.000 SGB's. But, we did cite McLean 2015 as an additional case series that may have used stronger methods than the 1992 study, but still is likely too small to detect rare events.
42	3	Page 10 , line 28 to 36 . potential complication rate of 33% should be addressed . #1 The needle used for the procedure is 18 Gauge , much larger than used by others 22 gauge and 25 gauge #2 Complications included were related to the procedure was 12% they included a increased pain after the placebo injection , a significant number of complications could potentially have been reduced with a smaller needle .	Added: "Complications included increased injection site pain, which could potentially have been reduced by using a smaller needle such as in prior studies (20 gauge in RCT vs 22-25 gauge in case series).
43	3	Page 10 , line 50 : Specific symptoms best responding to SGB have been studied by Dr Lynch :Specific symptoms affected by SGB in PTSD(Lynch)	Under heading of "who is most likely to benefit", starting on page 10, we added the findings from Lynch 2016: "Findings from a case series of 30 active duty military service members with combat-related PTSD suggest that people with predominantly hyperarousal and avoidance types of symptoms may be more likely to benefit from SGB.[cite Lynch 2016] But, this is very weak evidence as it is based on inference from evaluation of which symptoms are most impacted after SGB, rather than from direct comparison of response rates between people with different levels of these symptoms at baseline.
44	3	Page 11, line 34 : total of 27 veterans were treated via SGB (Navaie&Alkire 2014& Alkire 2015)	No change. Agreed that the small number of Veterans represents the minority of SGB's and is consistent with our statement that "Although most studies have been conducted in military populations, the majority were active-duty military members."

45	3	Page 11, lines 44 to 49 : Inadequate reporting of previous treatments , it is my view that all the patients we have seen in my clinic had access to the " gold standard " therapy and did not respond to the same , the criteria used by most researchers have been PCL-M and or CAPS to make sure the patient have the diagnosis of PTSD . Further in the publication by Dr Hoge titled" Interventions for War-Related Posttraumatic Stress Disorder Meeting Veterans Where They Are" is exactly on point , his conclusions were the following"However, veterans remain reluctant to seek care, with half of those in need not utilizing mental health services.3,4 Among veterans who begin PTSD treatment with psychotherapy or medication, a high percentage drop out, commonly 20% to 40% in randomized clinical trials (RCTs)5,6 but considerably higher in routine practice.3 The rate of recovery of 60% to 80% among treatment completers declines to around 40% when noncompleters are accounted for (using intention- to-treat analyses).5-7", basically the lack of current success due to what ever the reason does seem to require a new approach	We changed "Insufficient to support its use as adjuvant overall" to: "evidence is insufficient to support recommendations about *specifically when* to initiate SGB in the order of recommended conventional pharmacotherapies and psychotherapies. How much failed conventional therapy is "enough" before trying SGB? Although likely many study participants had already failed "gold standard" therapy and their lack of success suggested the need for an innovative approach, the studies' lack of specific criteria for establishing "failure" of conventional therapy, and/or dose and duration and order of conventional therapies makes it difficult for readers to compare their patient with those in the studies.
46	3	Page 12 , line 6 . Discussion of loss of PTSD diagnosis , this discussion is very complex due to implication for disability payment , a number of veterans treated did NOT wish to share their improvements with the VA hospitals	No change. One page 12, line 6, in the Limitations section, we are noting that the overall lack of assessment of remission (loss of PTSD diagnosis) is a limitation of all the studies as a whole, regardless of whether the participants were involved in disability evaluation. The point we are making is that loss of PTSD diagnosis is a desired outcome of any PTSD treatment and the studies should assess it.
47	4	p. 11, lines 31-32: "Overall, a key limitation the evidence on SGB is that it is based primarily on uncontrolled, unblinded studies." reads awkwardly. There needs to be a preposition between "limitation" and "the"; e.g. "Overall, a key limitation of the evidence on SGB is that it is based primarily on uncontrolled, unblinded studies."	Changed as suggested.
48	4	p. 11, lines 37-38: The majority of study participants were male, as in the VA, but mean age was late thirties to early forties and prevalence of depression, anxiety, pain, and other medical comorbidities were unclear." Prevalence is singular and were is plural; since "unclear" refers to prevalence and not the listing of comorbidities that follows prevalence in the sentence, I believe that the singular, was, should be used instead.	Changed as suggested.
49	4	p. 12, line 24: "…considerations such access to, contraindications for, and patient preference may guide SGB," a preposition between such and access is required, e.g. "such as access to…"	Changed to: "Other practical considerations that may guide treatment decisions include access to, contraindications for, and patient preference for SGB."

	1	I find myself in disagreement regarding the need for a large observational study. This would do little to reduce uncertainty regarding the benefits on the intervention though may be useful to outline possible harms. It is possible to conduct RCTs in this area and that should, in my view be the priority as it will afford the confidence to offer or withhold this intervention on the basis of effectiveness or lack thereof.	Changed to: "Both randomized trials and observational studies can contribute to our knowledge of SGB for PTSD."
50	2	Regarding risks, I think there should be some mention of cost of this procedure compared to an office visit for psychotherapy or medication.	Added to the Implications section: Cost of these innovative treatments compared to conventional psychotherapies and pharmacotherapies should also be assessed in the prioritization process. SGB costs have been estimated to be lower than conventional PTSD therapies ($2,000 for two SGB injections vs a range of $6,000 to $30,000).[Lipov 2012] But, we have not formally evaluated comparative costs or how these estimates apply to the current VA environment.
51	3	satisfaction and acceptance of the procedure is over 90%(McLean)	Added: "Finally, although those who have undergone SGB have found it highly acceptable,[McLean 2015] the invasive nature of SGB may be a barrier for some candidates to try it in the first place."
52	3	Biological markers have been reported to have impacted in PTSD patients such as PET scan(Alkire) and EEG in normal volunteers (Yeo) following SGB	As noted above, added Akire and Yeo studies to Background as references for information on biological markers.
53	3	No addiction or neurotoxicity of agents (vs MDMA, or Ketamine)	To our statement on pages 12-13 that "we did not investigate whether SGB should be a higher priority than other innovative treatments for PTSD, such as MDMA, ketamine or cranial electrical stimulation", we added "But, each has their own unique set of potential harms, such as addiction and neurotoxicity, that would have to be considered in relation to SGB's net benefits."
54	3	Speed of on set 30 minutes (presented at PGA 2011)	On page 5, changed "within minutes to days" to "within 30 minutes to days"
55	3	Please read Dr Summers review form John Hopkins for a excellent up to date information	Agreed and we have already cited Dr. Summers' review in the Discussion, along with other prior reviews, to confirm that we agree with the conclusions of previous reviews that further research is needed to more precisely determine the balance of benefits and harms of SGB for PTSD.
56	5	First report to review. Looks great.	Thank you.

REFERENCES

1. Hanling SR, Hickey A, Lesnik I, et al. Stellate Ganglion Block for the Treatment of Posttraumatic Stress Disorder: A Randomized, Double-Blind, Controlled Trial. *Regional Anesthesia & Pain Medicine*. Jul-Aug 2016;41(4):494-500.