TITLE: Anesthetic Injections Into the Stellate Ganglion for the Treatment of Hot Flashes in Women: A Review of Clinical and Cost-Effectiveness and Guidelines

DATE: 14 April 2014

CONTEXT AND POLICY ISSUES

Hot flashes, or hot flashes, are sudden and transient periods of feeling hot and sweating, with possible co-occurrence of palpitations and anxiety. Hot flashes occur in about 80% to 90% of post-menopausal women and in 51% to 81% of women with breast cancer.[1-3] The physiological mechanisms of hot flashes are still not clear but seem to involve neurochemical and thermoregulatory interruptions.[4-7] Generally, therapeutic options for hot flashes include pharmaceutical/hormone replacement therapies (e.g., estrogen and progesterone, antidepressants such as venlafaxine, anticonvulsants such as pregabalin, antiadrenergics such as clonidine, anticholinergics such as bellergal), nutraceutical therapies (e.g., herbals, vitamins, phytoestrogens), and complementary/behavioral therapies (e.g., acupuncture, yoga).[8,9] Stellate ganglion block (SGB), a procedure aiming to selectively block the sympathetic outflow from a stellate ganglion by injecting an anesthetic such as bupivacaine with fluoroscopic guidance around the ganglion, has been used as a treatment of migraines, atypical facial pain, upper extremity pain, and complex regional pain syndrome.[10] SGB recently emerged as a surgical therapy for hot flashes based on the belief that interruptions of the connections between a stellate ganglion and areas of the central nervous system may induce the reset of the body temperature mechanisms.[10-12]

This Rapid Response report aims to review the clinical, cost effectiveness and guidelines of the use of SGB in the treatment of hot flashes in women.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of anesthetic injections into the stellate ganglion for the treatment of hot flashes in women?

2. What is the cost-effectiveness associated with anesthetic injections into the stellate ganglion for the treatment of hot flashes in women?

3. What are the guidelines associated with anesthetic injections into the stellate ganglion for the treatment of hot flashes in women?

KEY FINDINGS

Limited evidence has shown that SGB may provide an effective treatment in reducing the frequency and severity of hot flashes in post-menopausal women and in women with breast cancer in the short term. Larger sham controlled trials are needed to confirm the findings. There is no evidence on cost-effectiveness of CBG and guidelines associated with its use are lacking.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and March 14, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of any relevant titles or abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Women experiencing hot flashes
Intervention	Anesthetic (any kind) injection into the stellate ganglion
Comparator	No intervention or status quo (hormonal therapy)
Outcomes	Clinical effectiveness Cost-effectiveness Guidelines
Study Designs	Health technology assessments (HTA), systematic reviews (SRs), and meta-analyses (MAs), randomized controlled trials (RCTs), non-RCTs, economic evaluations, guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2009, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included trials was assessed using the Downs and Black checklist.[13] Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 31 citations. After screening of abstracts from the literature search and from other sources, 14 potentially relevant studies were selected for full-text review. Five studies related to the use of anesthetic injections into the stellate ganglion for the treatment of hot flashes in women were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included study is provided in Appendix 2.

Study design

Among the included studies, two were RCTs with patients[14] or patients and assessors[15] blinded to the intervention, and three were observational open uncontrolled studies.[16-18]

Population

The identified studies included post-menopausal women[14,16] or breast cancer survivors[15,17,18] with moderate to severe vasomotor symptoms (hot flashes and night sweats).

Interventions and comparators

The intervention was SGB using bupivacaine in all included trials.[14-18] Comparators were sham injection with saline,[14] or pregabalin[15] in the included RCTs. For the observational studies, outcomes difference from baseline was measured.[16-18]

Outcomes

Reported outcomes in the included studies were frequency[14-18] and intensity of hot flashes,[14,16] adverse events,[14,18] sleep,[14,16,17] and quality of life.[14,16]

Summary of Critical Appraisal

Two included studies were randomized and controlled trial in which patients[14] or patients and outcome assessors[15] were blinded to the intervention, and three studies were observational open uncontrolled trials.[16-18] All trials had a small population (the largest enrolled 40 participants) and short follow-up time (longest 6 months). Hypotheses, method of population selection, main outcomes, interventions, patients characteristics, main findings clearly described in all included trials. Four studies did not indicate whether there was sufficient power to detect a clinically

important effect,[15-18] and four studies did not report losses to follow-up.[14-17] The small populations and short follow-up time caution the generalizability of the findings and the strength of the evidence. Authors in one study received honoraria from the industry for consulting on non-hormonal treatment of hot flashes.[14]

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

1. What is the clinical effectiveness of anesthetic injections into the stellate ganglion for the treatment of hot flashes in women?

The literature search found two RCTs,[14,15] and three observational uncontrolled studies[16-18] that examined the clinical effectiveness of SGB for the treatment of hot flashes in women with a follow-up time up to six months. In general, SGB was effective in reducing the frequency and severity of hot flashes in post-menopausal women and in women with breast cancer. Controlled studies with a comparator showed SGB superior to placebo or pregabalin 75mg twice/daily.

A patient-blinded, controlled study randomized 40 post-menopausal women to SBG or sham injection with saline.[14] Frequencies of subjective (measured by daily diary) and objective (measured by ambulatory skin conductance monitors) hot flashes and night sweat (i.e., vasomotor syndrome or VMS), adverse events related to SGB, depression, sleep, and quality of life were evaluated and compared for six months. There were no statistically significant differences in overall (mild, moderate and severe hot flashes) subjective VMS frequencies between the two groups, but the frequency of moderate to very severe VMS was reduced more in the SGB group compared with the sham control group (50% reduction in event rate; $P < 0.001$). The frequency of objective VMS was also reduced in the SGB group than in the sham control group (29% reduction in event rate; $P < 0.05$). There were no SBG-related serious adverse events. There was no statistically significant difference between the two groups in depression, sleep quality, and quality of life.

A patient and assessor-blinded controlled study randomized 40 breast cancer patients to SBG or pregabalin 75mg twice/daily.[15] During the 3-month study, the frequencies of mild, moderate, and severe hot flashes as measured by daily diaries in the SBG group were reduced compared to the pregabalin group ($P < 0.05$).

An observational open uncontrolled study of 20 post-menopausal women with hot flashes examined the difference from baseline in hot flash frequency and severity as measured by daily diaries during a 4-week study.[16] Flash score is the product of hot flash frequency and hot flash severity. There were statistically significant reductions in flash frequency and flash score from baseline (from 14 ± 0.8 to 10 ± 1.1; $P = 0.003$ and from 33 ± 2.8 to 21 ± 2.4; $P = 0.002$, respectively) There was no statistically significant reduction in flash severity from baseline ($P = 0.212$). There was improvement on sleep quality and quality of life from baseline but statistical significance is inconsistent depending on the scale used.

Two observational open uncontrolled studies of a total of 28 breast cancer women with hot flashes examined the difference from baseline in hot flash frequencies, hot flash score, sleep

and adverse events as measured by daily diaries during a 24-week study[17] and a 6-week pilot study.[18] A statistically significant reduction from baseline in hot flash score (47% reduction, *P* = 0.03) and improvement in sleep quality (odds ratio 4.3; *P* = 0.03) was observed in one study after 24 weeks follow-up.[17] The pilot study also showed a reduction of hot flashes and score at six weeks (*P* values not reported), with no adverse events reported.[18]

2. What is the cost-effectiveness associated with anesthetic injections into the stellate ganglion for the treatment of hot flashes in women?

There is no evidence found on the cost-effectiveness of anesthetic injections into the stellate ganglion for the treatment of hot flashes in women.

3. What are the guidelines associated with anesthetic injections into the stellate ganglion for the treatment of hot flashes in women?

The literature search did not find any guidelines associated with anesthetic injections into the stellate ganglion for the treatment of hot flashes in women.

Limitations

Evidence on the effectiveness of SBG is limited from a small number of trials, most of them uncontrolled, with small sample size and short follow-up periods. Since evaluation of hot flash frequencies and severity were mainly subjective, controlled studies with comparator are needed to balance out the placebo effect of the intervention. A more comprehensive evaluation of the clinical effectiveness of SBG would be achieved with trials comparing SBG to different therapeutic options for hot flashes.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Findings from studies with small sample sizes and short follow-up periods showed that SGB may provide an effective treatment in reducing the frequency and severity of hot flashes in post-menopausal women and in women with breast cancer in the short term. Larger placebo-controlled trials are needed to confirm the findings. There is no evidence on cost-effectiveness of CBG and guidelines associated with its use are missing.

Despite the fact that a positive effect of SGB on reducing hot flashes was first reported since 2005 in a pilot study on menopausal women,[19] then in 2008 in another pilot study in women with a history of breast cancer,[20] and has continued to be demonstrated in the recent studies included in this report, there is no clinical guideline on the use of this procedure for women with hot flashes. Although the prevalence of its use in routine practice is unclear, it is reasonable to conclude that SGB has passed its experimental phase and that its use has brought relief to women with hot flashes. In addition, SGB does not carry the potential systemic side effects associated with the use of pharmaceutical therapies, especially long-term hormonal therapy, but it is costly, ranging from US$1,000 to $3,000 per procedure in the US.[21] The decision to use SBG for hot flashes may depend on the cost-effectiveness of the procedure.

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REFERENCES

1. Kronenberg F. Hot flashes: epidemiology and physiology. Ann N Y Acad Sci. 1990;592:52-86.

2. Freeman EW, Sherif K. Prevalence of hot flushes and night sweats around the world: a systematic review. Climacteric. 2007 Jun;10(3):197-214.

3. Harris PF, Remington PL, Trentham-Dietz A, Allen CI, Newcomb PA. Prevalence and treatment of menopausal symptoms among breast cancer survivors. J Pain Symptom Manage. 2002 Jun;23(6):501-9.

4. Kronenberg F, Cote LJ, Linkie DM, Dyrenfurth I, Downey JA. Menopausal hot flashes: thermoregulatory, cardiovascular, and circulating catecholamine and LH changes. Maturitas. 1984 Jul;6(1):31-43.

5. Freedman RR. Biochemical, metabolic, and vascular mechanisms in menopausal hot flashes. Fertil Steril. 1998 Aug;70(2):332-7.

6. Carpenter JS. State of the science: hot flashes and cancer. Part 1: definition, scope, impact, physiology, and measurement. Oncol Nurs Forum. 2005 Sep;32(5):959-68.

7. Kronenberg F. Hot flashes: phenomenology, quality of life, and search for treatment options. Exp Gerontol. 1994 May;29(3-4):319-36.

8. Fisher WI, Johnson AK, Elkins GR, Otte JL, Burns DS, Yu M, et al. Risk factors, pathophysiology, and treatment of hot flashes in cancer. CA Cancer J Clin. 2013 May;63(3):167-92.

9. Kontos M, Agbaje OF, Rymer J, Fentiman IS. What can be done about hot flushes after treatment for breast cancer? Climacteric. 2010 Feb;13(1):4-21.

10. 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). Med Hypotheses. 2009 Jun;72(6):657-61.

11. Pachman DR, Jones JM, Loprinzi CL. Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. Int J Womens Health [Internet]. 2010 [cited 2014 Mar 19];2:123-35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2971731/pdf/ijwh-2-123.pdf

12. Guttuso T, Jr. Stellate ganglion block for treating hot flashes: a viable treatment option or sham procedure? Maturitas. 2013 Nov;76(3):221-4.

13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2014 Apr 9];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

14. Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM. Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women. Menopause. 2014 Feb 3. Epub ahead of print.

15. Othman AH, Zaky AH. Management of hot flushes in breast cancer survivors: comparison between stellate ganglion block and pregabalin. Pain Med. 2014 Mar;15(3):410-7.

16. van Gastel P, Kallewaard JW, van der ZM, de BH. Stellate-ganglion block as a treatment for severe postmenopausal flushing. Climacteric. 2013 Feb;16(1):41-7.

17. Haest K, Kumar A, Van Calster B, Leunen K, Smeets A, Amant F, et al. Stellate ganglion block for the management of hot flashes and sleep disturbances in breast cancer survivors: an uncontrolled experimental study with 24 weeks of follow-up. Ann Oncol [Internet]. 2012 Jun [cited 2014 Mar 19];23(6):1449-54. Available from: http://annonc.oxfordjournals.org/content/23/6/1449.full.pdf+html

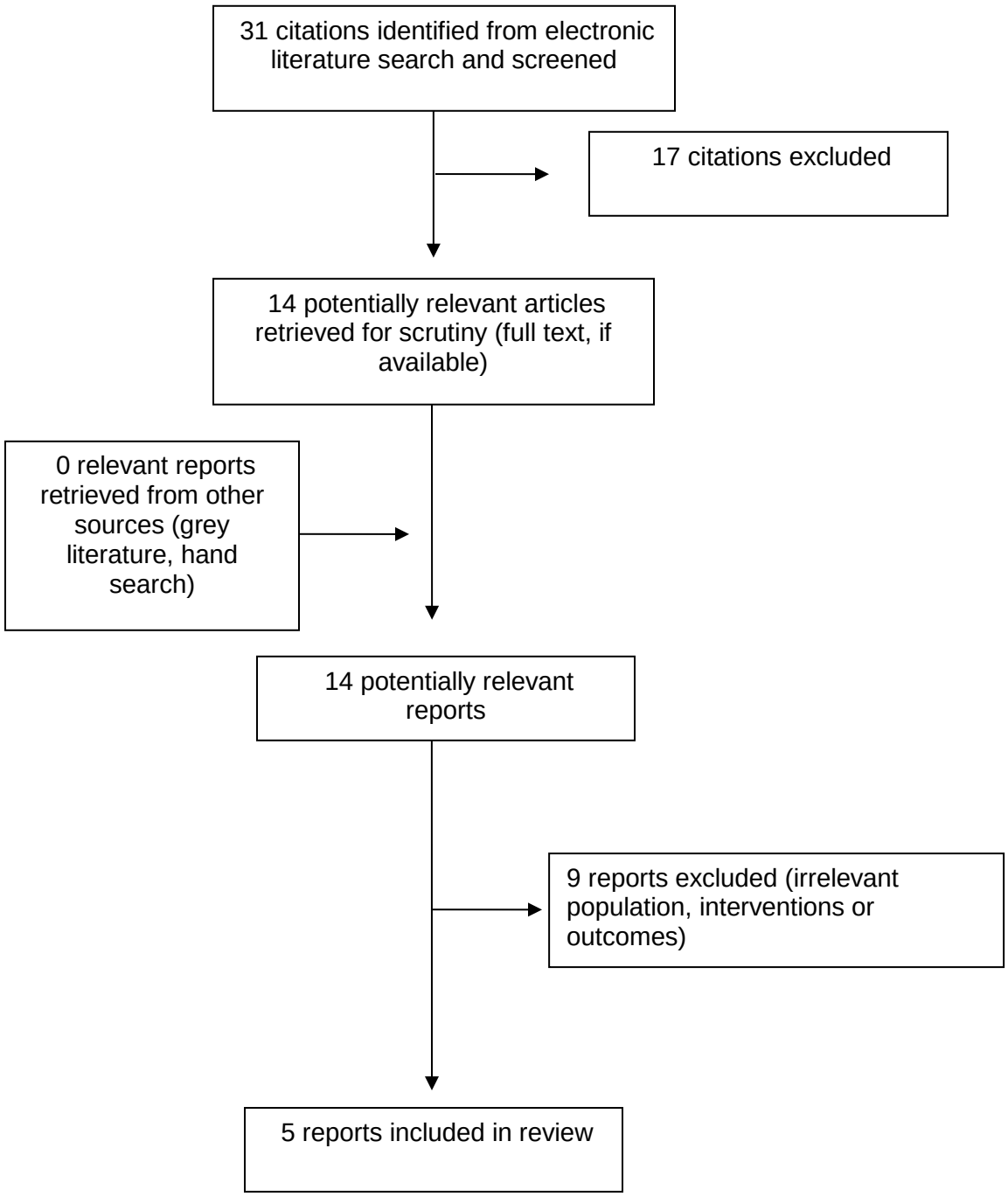
18. Pachman DR, Barton D, Carns PE, Novotny PJ, Wolf S, Linquist B, et al. Pilot evaluation of a stellate ganglion block for the treatment of hot flashes. Support Care Cancer [Internet]. 2011 Jul [cited 2014 Mar 19];19(7):941-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3107341/pdf/nihms-274998.pdf

19. Lipov E, Lipov S, Stark JT. Stellate ganglion blockade provides relief from menopausal hot flashes: a case report series. J Womens Health (Larchmt). 2005 Oct;14(8):737-41.

20. Lipov EG, Joshi JR, Sanders S, Wilcox K, Lipov S, Xie H, et al. Effects of stellate-ganglion block on hot flushes and night awakenings in survivors of breast cancer: a pilot study. Lancet Oncol. 2008 Jun;9(6):523-32.

21. Loprinzi CL, Barton DL, Carns PE. Stellate-ganglion block: a new treatment for hot flushes? Lancet Oncol. 2008 Jun;9(6):506-7.

Appendix 1: Selection of Included Studies



Appendix 2: Summary of Included Study Characteristics

Table A1: Characteristics of Included studies

First Author, Year, Country,	Design, Sample Size, Patient Characteristics, Length of Follow-up Sponsorship	Intervention	Comparator(s)	Main Study Outcomes
Walega,[14] 2014, US	RCT, patients blinded to group assignment; 40 post-menopausal women with moderate to severe VMS (i.e., hot flashes and night sweats); 6 months follow-up; authors received honoraria from the industry for consulting on non-hormonal treatments of VMS	SGB with bupivacaine	Sham injection with saline	Frequencies of total subjective VMS (measured by daily diaries) Frequencies of objective VMS (measured by ambulatory skin conductance monitors) VSM intensity (subjective, by diary; calculated as a product of frequency and severity) Sleep Quality of life Adverse events
Othman,[15] 2014, Egypt	RCT; patients and assessors blinded to group assignment; 40 breast cancer survivors with hot flashes; 3 months follow-up; no conflict of interest	SGB with bupivacaine	Pregabalin 75 mg twice daily	Frequencies of hot flashes
Gastel,[16] 2013, The Netherlands	Observational open uncontrolled study; 20 post-menopausal women with hot flashes; 4 weeks follow-up; no conflict of interest	SGB with bupivacaine	No comparator	Frequencies of hot flashes Hot flash intensity Hot flash score Sleep Quality of life
Haest,[17] 2012, Belgium	Observational open uncontrolled study; 34 breast cancer survivors with severe VMS; 24 weeks follow-up; no conflict of interest	SGB with bupivacaine	No comparator	Hot flash score Sleep
Pachman,[18] 2011, US	Observational open uncontrolled study; 8 breast cancer survivors with hot flashes; 6 weeks follow-up; no conflict of interest	SGB with bupivacaine	No comparator	Frequencies of hot flashes Hot flash score Adverse events

RCT: randomized controlled trial; SGB: stellate ganglion block; VMS: vasomotor symptoms

Appendix 3: Summary of Critical Appraisal of Included Study

Table A2: Summary of Critical Appraisal of Included Study		
First Author, Publication Year	**Strengths**	**Limitations**
Critical appraisal of included trials (Downs and Black[13])		
Walega,[14] 2014	• hypothesis clearly described • patients randomized • patients blinded to intervention • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • study had sufficient power to detect a clinically important effect	• assessors not blinded to intervention • losses to follow-up not described
Othman,[15] 2014	• hypothesis clearly described • patients randomized • patients and assessors blinded to intervention • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided	• unclear whether study had sufficient power to detect a clinically important effect • losses to follow-up not described
Gastel,[16], 2013	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided	• patients not randomized • no blinding possible • unclear whether study had sufficient power to detect a clinically important effect • losses to follow-up not described
Haest,[17] 2012	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided	• patients not randomized • no blinding possible • unclear whether study had sufficient power to detect a clinically important effect • losses to follow-up not described
Pachman,[18] 2011	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • losses to follow-up described	• patients not randomized • no blinding possible • unclear whether study had sufficient power to detect a clinically important effect • estimates of random variability and actual probability values not provided

Appendix 4: Main Study Findings and Authors' Conclusions

Table A3: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical effectiveness of anesthetic injections into the stellate ganglion for the treatment of hot flashes in women)		
Walega,[14] 2014	Total subjective VMS frequency (reduction from baseline) No statistical difference in reduction between SGB and sham control groups. Moderate to severe subjective VMS frequency: RRR (ratio of event rate ratio between the 2 groups) 0.50 (95% CI 0.35, 0.71); *P* < 0.001 in favour of SBG Total objective VMS frequency: RRR (ratio of event rate ratio between the 2 groups) 0.71 (95% CI 0.64, 0.99); *P* < 0.05 in favour of SGB Subjective VSM intensity (difference from baseline): Months 4 to 6: 38% reduction in SBG group; 8% reduction in sham control group (*P* = 0.04) Adverse events: 0 Depression, sleep, quality of life: no statistically significance difference between the 2 groups	*"SGB may provide effective treatment of VMS in women who seek nonhormonal treatments because of safety concerns and personal preference. The finding that SGB significantly reduces objectively measured VMS provides further evidence of efficacy. A larger trial is warranted to confirm these findings"* (p 1e)
Othman,[15] 2014	Statistically significant (*P* < 0.05) reduction in the frequency of mild, moderate, severe and total hot flashes in SGB group compared to pregabalin group	*"The stellate ganglion block had superior efficacy in the management of hot flashes in breast cancer survivors"* (p 410)
Gastel,[16] 2013	Statistically significant reduction in flash frequency from baseline (14 ± 0.8 to 10 ± 1.1; *P* = 0.003) Statically significant reduction in flash score from baseline (33 ± 2.8 to 21 ± 2.4; *P* = 0.002) Improvement on sleep and quality of life from baseline; statistical significance is inconsistent depending on the scale used No statistically significant reduction in flash severity from baseline (*P* = 0.212)	"*The results of this study support the observation that SGB may be a useful therapy for a subset of women with severe postmenopausal flashing. A sham-controlled, single-blinded study is warranted to improve the evidence of efficacy*" (p 41)
Haest,[17] 2012	Statistically significant reduction in hot flash score from baseline at 1 week (64% reduction; *P* < 0.0001) and at 24 weeks (47% reduction; *P* = 0.03) Statistically significant improvement in sleep quality from baseline at 1 week (odd ratio 3.4; 95% CI 1.6, 7.2; *P* = 0.0002) and at 24 weeks (odd ratio 4.3; 95% CI 1.9, 9.8; *P* = 0.03)	*"In the short term, SGB appears to be an effective treatment with acceptable morbidity for some breast cancer survivors with therapy-resistant vasomotor symptoms and/or sleep disturbances. Although sleep quality was maintained out to 24 weeks the efficacy of SGB for hot flashes was reduced over time. A randomized controlled trial is needed to confirm these findings"* (p 1449)
Pachman,[18] 2011	Reduction of hot flash frequency and score (both 60%) from baseline at 6 weeks (*P* values not reported)	*"The results of this pilot trial support that stellate ganglion blocks may be a helpful therapy for*

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
	No SBG-related significant adverse event reported	*hot flashes. A prospective placebo-controlled clinical trial should be done to more definitively determine this contention"* (p 941)
Research question 2 (cost-effectiveness associated with anesthetic injections into the stellate ganglion for the treatment of hot flashes in women)		
No evidence found		
Research question 3 (guidelines associated with anesthetic injections into the stellate ganglion for the treatment of hot flashes in women)		
No evidence found		

SGB: stellate ganglion block; VMS: vasomotor syndrome