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Nonpharmacologic Treatments for Menopause-associated Vasomotor Symptoms

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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ABSTRACT

INTRODUCTION

Vasomotor symptoms (VMS), which include hot flashes and night sweats, are the most common symptoms reported during the menopausal transition and are experienced by as many as 80% of women. VMS can lead to increased healthcare encounters for symptom relief and reductions in quality of life. The degree to which VMS is bothersome is determined not only by how frequently it occurs but also by other factors such as duration of VMS, coexisting sleep problems, and the extent to which VMS interferes with daily activities or job-related activities. Hormone therapy (HT) is an effective treatment for reducing VMS, but use of this therapeutic approach must be individualized through weighing benefits with known risks, such as cardiovascular events or uterine and breast cancers. Based on age (> 45 years), currently half of the approximately 360,000 women Veterans who use Veterans Health Administration healthcare are perimenopausal or postmenopausal. Due in part to concerns about possible harms from long-term hormone therapy and in part to uncertain efficacy and safety of pharmacologic treatments, many women with VMS seek nonhormonal, nonpharmacologic treatment options.

METHODS

We developed the following research question in consultation with our stakeholders and a panel of technical experts:

> In women with vasomotor symptoms (VMS) that are associated with perimenopause or postmenopause, what are the effects on VMS, health-related quality of life, and adverse effects of the following nonpharmacologic, nonhormonal interventions: acupuncture; yoga, tai chi, and qigong; structured exercise; and meditation, mindfulness, hypnosis, and relaxation?

Given the multiple high-quality systematic reviews (SRs) in this topic area, we chose a method commonly known as an umbrella review, or review of reviews. We supplemented this approach by also evaluating randomized controlled trials (RCTs) published after the most recent good-quality SR for each of the eligible interventions. We grouped SRs and RCTs by intervention category. We graded the quality of SRs and new RCTs and prioritized the highest-quality SRs. Good-quality reviews had no important limitations and fair reviews had at least some important limitations. We reported intervention effects separately for inactive and active comparators and examined SRs for relevant subgroup analyses. When a new meta-analysis was indicated and feasible, we computed summary estimates of effect for each intervention. We explored the 2 primary outcomes: VMS and health-related quality of life. We assessed strength of evidence using the approach described in the Agency for Healthcare Research and Quality's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*

RESULTS

We identified 239 unique SR citations; of these, 37 were retrieved for full-text review, and 10 were retained for data abstraction. We also identified 1135 unique RCTs; of these, 67 were retrieved for full-text review, and 14 articles plus 2 companion papers were retained for data

abstraction. The 10 SRs addressed acupuncture (n = 3), yoga (n = 1), structured exercise (n = 1), and meditation, mindfulness, hypnosis, relaxation, or mixed interventions (n = 5). The 14 new RCTs evaluated acupuncture (n = 4), yoga (n = 2), structured exercise (n = 3), and meditation, mindfulness, hypnosis, relaxation, or mixed interventions (n = 6). All studies reported the effects of interventions on VMS; quality of life and other outcomes were reported less frequently.

Acupuncture

We identified one good-quality SR published in 2013 that included women with VMS from any cause and 2 fair-quality SRs that included only women with any type of cancer. The good-quality SR included 15 relevant RCTs comprising 1127 participants. Comparison groups were no acupuncture, sham acupuncture, hormone therapy, or relaxation. Duration of acupuncture treatments ranged from 4 to 12 weeks across the RCTs. Traditional acupuncture was administered in 11 trials, electroacupuncture in 3 trials, and a combination of acupuncture and auricular acupuncture in a single trial. Twelve RCTs reported daily VMS by a self-report symptom diary. The remaining 3 assessed daily VMS frequency and severity as a hot flash score. Three RCTs assessed menopause-related symptoms considered by the authors of the SR to reflect quality of life. Applying the Cochrane guidance for overall risk of bias, 2 RCTs were rated as low risk and 11 were rated as high risk. This SR did not address durability of effect.

We identified 4 relevant RCTs with low risk of bias published since 2012 that were not included in the eligible SRs. Three examined the effect of acupuncture on VMS in perimenopausal and postmenopausal women, and one examined the effects of electroacupuncture in breast cancer survivors compared with the drug gabapentin, a placebo pill, or sham acupuncture. All 4 of these RCTs examined durability of effect. Three of the 4 new RCTS found that reductions in Hot Flash Composite Score and hot flash frequency were maintained at 12, 16, and 24 weeks posttreatment, respectively.

Our updated meta-analyses suggest that acupuncture is effective at reducing VMS frequency (SMD -0.66, 95% CI -1.06 to -0.26, I^2 = 61.7%, 5 trials) and VMS severity (SMD -0.49, 95% CI -0.85 to -0.13, I^2 = 18.1%, 4 trials), and improving quality of life (SMD 0.93, 95% CI -1.20 to -0.67, I^2 = 0.0%, 3 trials) when compared with no acupuncture, but not when compared with sham acupuncture. This translates to an average of 3 fewer hot flashes daily. Two of 4 trials reported that treatment benefit was maintained 16 to 24 weeks after end of treatment. The other 2 trials did not show sustained effects. Meta-analysis also suggests that acupuncture is associated with higher daily VMS frequency compared with hormone therapy (SMD 3.18, 95% CI 2.06 to 4.29, I^2 = 0%, 3 trials). Acupuncture and hormone therapy, however, are associated with similar changes in VMS severity (SMD 0.53, 95% CI -0.14 to 1.20, 2 trials).

Yoga, Tai Chi, and Qigong

We identified a single good-quality SR published in 2012 that included 5 RCTs (582 participants) evaluating the effect of yoga on VMS when compared with both inactive and/or active comparators. Yoga interventions were delivered in 34 to 40 sessions over 8 weeks to 4 months. All 5 interventions included yoga postures and meditation; 4 included breathing exercises, and 2 included lifestyle lectures. Risk of bias was determined to be low risk for 2 RCTs and high risk for 3 RCTs. Only one study included in the SR examined durability of effect

at 12 weeks post-treatment. We did not identify any eligible SRs that evaluated the effectiveness of tai chi or qigong.

We also identified 2 new relevant RCTs that assessed the impact of yoga on hot flash frequency and severity and quality of life among 102 perimenopausal or postmenopausal women, but both were judged to be of high risk of bias. In these, integral yoga or a Rusie Dutton course lasting 10 or 13 weeks was compared with inactive controls. Sessions were held weekly for 90 minutes. Outcomes were assessed using the Daily Hot Flash Diary and the Global Quality of Life Scale at 5 and 10 weeks in one RCT and subscales from the Menopause-specific Quality of Life instrument at 12 weeks in the other RCT. Neither of the new RCTs examined durability of treatment effects beyond the end of treatment. We did not identify any new RCTs that evaluated the effectiveness of tai chi or qigong.

The authors of the SR did not find an association between yoga and a reduction in VMS. We conducted an updated meta-analysis examining the effect of yoga compared with active and inactive controls on hot flash severity change scores using data from 2 new RCTs and 2 RCTs included in the SR. Results suggest that yoga is significantly associated with a reduction in hot flash severity (SMD -0.36, 95% CI -0.65 to -0.07, I^2 = 0.0%, 4 trials). Quality of life was not examined frequently. The single, small RCT that suggested some improvement in quality of life was statistically inconclusive.

Structured Exercise

We identified one good-quality and one fair-quality SR, both published in 2014, that included comparative evaluations of exercise, mindfulness, and relaxation. The good-quality SR included 5 RCTs that involved 762 sedentary, perimenopausal or postmenopausal women with VMS. In the majority of studies (n = 4), exercise was conducted with supervision or in a group session. The number and length of planned sessions ranged from 12 to 96 sessions over 12 to 36 weeks. The risk of bias was judged by the authors of the SR to be high risk for 4 RCTs and low risk for one RCT. The authors of the SR concluded there was no evidence that exercise reduced hot flash frequency or severity compared with inactive control (n = 4), yoga (n = 2), or hormone therapy (n = 1). Our updated meta-analyses did not find significant effects of structured exercise for either VMS frequency (SMD -0.08, 95% CI -0.33 to 0.16, I^2 = 0.0%, 4 trials) or severity (SMD -0.06, 95% CI -0.21 to 0.10, I^2 = 0.0%, 5 trials) compared with inactive control.

We identified 2 new RCTs that examined the effect of exercise compared with inactive control for VMS among perimenopausal or postmenopausal women. Both trials were judged to be low risk of bias. One studied women after breast cancer treatment exclusively. Exercise interventions were individually tailored programs focusing on aerobic exercise sessions lasting 40 to 90 minutes for 12 to 24 weeks. VMS was assessed using the Hot Flash Rating Scale in both trials. One RCT reported menopause-specific quality of life and found significantly lower sleep problem scores at 6 months' follow-up. The other trial found moderate benefit from structured exercise on health-related quality of life at end of treatment (effect size 0.46) and 12 weeks later (effect size 0.41).

Meditation, Mindfulness, Hypnosis, and Relaxation

We identified 5 SRs (2 good-quality, 3 fair-quality) that met eligibility criteria. One SR examined relaxation and mindfulness, one examined hypnosis exclusively, and 3 reported on mixed interventions. Of the RCTs included in the SRs, only one evaluated mindfulness-based stress reduction, and none assessed the effects of meditation. We focused on both the good-quality 2014 Cochrane Collaboration SR that addressed relaxation and paced respiration in 281 women with VMS and the fair-quality 2015 SR examining hypnosis in 274 women with breast cancer.

In the good-quality SR, 4 RCTs assessed VMS frequency, Kupperman Index scores, and mood. No studies reported on quality of life or adverse effects. Time of final follow-up assessment varied across RCTs from 4 weeks to 24 weeks with only one trial completing a follow-up assessment after completion of the intervention. No significant difference in reduction of hot flash frequency was found between any type of relaxation or mindfulness interventions compared with control groups for the primary outcomes of VMS frequency or quality of life. Authors of the SR did not report an overall risk of bias rating for individual studies but noted that the overall quality of evidence was “very low.”

In the fair-quality SR, 3 RCTs included the comparators of attention control, no treatment, and gabapentin. Outcomes measured included VMS frequency, health-related quality of life, mood, and adverse effects. The timing of outcome assessments was unclear for these trials. This SR presented qualitative findings only and found a significant decrease in hot flashes among women treated with hypnosis compared with no treatment; however, there was no difference when compared with gabapentin. Authors reported an overall low risk of bias in the included studies using the Cochrane Risk of Bias tool.

We identified 6 new RCTs that were not included in existing SRs. Three examined paced respiration and 3 examined effects of applied relaxation on VMS or quality of life among perimenopausal or postmenopausal women. Of the 3 new relaxation RCTs, one was low risk of bias, one was unclear risk, and one was high risk. We conducted a new meta-analysis comparing paced respiration with a control group. We found that paced respiration is not associated with a statistically significant decrease in hot flash frequency (SMD 0.04, 95% CI -0.73 to 0.82, I^2 = 56.6%) or severity (SMD 0.06, 95% CI -0.69 to 0.80, I^2 = 65.1%).

In general, our secondary outcomes of interest—sleep quality, depression, anxiety, and adverse effects—were rarely reported in the SRs addressing relaxation, and the results were mixed when they were reported.

CONCLUSION

Compared with waitlist controls, RCTs support acupuncture and yoga for reducing VMS and the impact of such symptoms on women’s activities and health-related quality life. The strength of evidence, however, is low to moderate. Moderately good evidence shows no benefit from structured exercise for VMS. The evidence in support of the effectiveness of mindfulness or relaxation is mixed, with some promising evidence that needs replication for hypnosis. There is insufficient evidence to draw conclusions about the effectiveness of these nonpharmacologic therapies for improving sleep, depression, or anxiety. The safety of the nonpharmacologic,

nonhormonal approaches evaluated in this report has not been rigorously examined, but there is no clear signal for a significant potential for harm. Overall, most of the data included in this report comes from smaller studies with homogenous participant populations. Larger trials of populations more reflective of the diversity of women experiencing VMS will be necessary to discern the effectiveness of nonpharmacologic interventions in symptomatic menopausal women.

ABBREVIATIONS TABLE

AHRQ	Agency for Healthcare Research and Quality
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
ESP	Evidence-based Synthesis Program
MD	Mean difference
MeSH	Medical Subject Heading
PICOTS	Population, intervention, comparator, outcome, timing, setting
RCT	Randomized controlled trial
SMD	Standardized mean difference
SOE	Strength of evidence
SR	Systematic review
VA	Veterans Affairs
VMS	Vasomotor symptoms
VHA	Veterans Health Administration