Variation in menopausal vasomotor symptoms outcomes in clinical trials: A systematic review

Running title: Variation in reported menopausal vasomotor symptoms

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.15990

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Abstract

**Background:** There is substantial variation in how menopausal vasomotor symptoms are reported and measured among intervention studies. This has prevented meaningful comparisons between treatments and limited data synthesis.

**Objectives:** To systematically review outcome reporting and measures used to assess menopausal vasomotor symptoms from randomised controlled trials of treatments.

**Search Strategy:** We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials from inception to May 2018.

**Selection criteria:** Randomised controlled trials with a primary outcome of menopausal vasomotor symptoms in women and a sample size of at least 20 women per study arm.

**Data Collection and analysis:** Data about study characteristics, primary vasomotor related outcomes and methods of measuring them.

**Main results:** The search identified 5,591 studies, 214 of which were included. Forty-nine different primary reported outcomes were identified for vasomotor symptoms and 16 different tools had been used to measure these outcomes. The most commonly reported outcomes were frequency (97/214), severity (116/214) or intensity (28/114) of vasomotor symptoms or a composite of these outcomes (68/214). There was little consistency in how the frequency and severity/intensity of vasomotor symptoms were defined.

**Conclusions:** There is substantial variation in how menopausal vasomotor symptoms have been reported and measured in treatment trials. Future studies should include standardized outcome measures which reflect the priorities of patients, clinicians and researchers. This is most effectively achieved through the development of a Core Outcome Set. This systematic review is the first step towards development of a Core Outcome Set for menopausal vasomotor symptoms.

**Funding:** SI is funded by an MRC postdoctoral fellowship (MR/N015177/1). MH is funded by an NHMRC Practitioner Fellowship APP 1058935 and GDM is supported by an NHMRC Principal Research Fellowship APP1121844.
Keywords: vasomotor symptoms; menopause; core outcomes; randomised clinical trials

Tweetable summary: Menopausal hot flushes and night sweats have been reported in 49 different ways in clinical research. A core outcome set is urgently required.
Introduction

There is general agreement that vasomotor symptoms (hot flushes and night sweats) are the most common and problematic menopausal symptom\(^1\), \(^2\). Vasomotor symptoms are also the leading patient priority for treatment\(^3\). Oestrogen containing menopausal hormone therapy (MHT) is an effective treatment for menopausal vasomotor symptoms, however, use of MHT has substantially fallen following concerns about safety\(^4\). There is a growing focus on the development and evaluation of non-pharmacological and non-hormonal treatments for vasomotor symptoms\(^5\). In addition, MHT is contraindicated in women with a personal history of breast cancer who may report more severe vasomotor symptoms than women experiencing natural menopause\(^6\). Enhanced understanding of the central mechanisms regulating vasomotor symptoms is driving the development and evaluation of novel targeted therapies\(^7\), but the interpretation and implementation of these studies is hampered by lack of consensus about how vasomotor symptoms should be reported and measured. This limits the potential to compare treatments and to synthesise the evidence, which in turn compromises decision-making by clinicians and patients.

Current National Institute for Health and Care Excellence (NICE) guidelines on the management of menopause\(^8\) highlight the need for greater standardisation of outcome reporting and measures for treatment trials in menopause and the consequent difficulty in evidence synthesis. There is an urgent need to determine what outcomes are most important to patients, clinicians and researchers in order to increase the relevance of future intervention studies and facilitate comparisons between treatments\(^9\), \(^10\). The Core Outcomes in Effectiveness (COMET) initiative is leading protocols for the development of Core Outcome Sets. These are well defined, condition specific and feasible outcomes which should be included as a minimum set of outcomes in intervention studies \(^11\). To progress the development of Core Outcome sets in women’s health\(^12\), 80 editors of women’s health journals have formed a consortium to support the development, dissemination and implementation of core outcome sets within the reproductive field (Core Outcomes in Women's and Newborn Health-CROWN, http://www.crown-initiative.org)\(^13\).
The Core Outcomes in Menopause (COMMA) initiative is an international consortium of clinicians, researchers and consumers developing a Core Outcome Set for menopausal symptoms. Following a standardised process, we have first systematically reviewed all randomised controlled trials (RCTs) of interventions for menopausal vasomotor symptoms to determine what outcomes have been reported and how they have been measured. We will then repeat this process for vaginal symptoms at menopause. This information will then be used to inform a Delphi survey by clinicians, researchers and patients to identify priorities for inclusion in the final Core Outcome Set.

**Methods**

**Study eligibility**

We included all RCTs with a primary outcome of female menopausal vasomotor symptoms and a sample size of at least 20 women per study arm to minimize the likelihood of including feasibility or pilot studies. We excluded studies that assessed menopausal vasomotor symptoms as a secondary outcome, quasi-randomized studies, secondary analyses of previously published RCTs, conference abstracts of RCTs, observational, analytical, or diagnostic studies and feasibility/pilot studies. We also excluded studies primarily aiming to assess pharmacokinetics, the mechanism of drug action, or tolerability and intervention studies with no explicit sample size calculations.

**Search strategy**

We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) until May 2018. We hand searched the reference lists of the included trials or other keynote publications. Search terms included menopause, menopausal, menopausal symptoms, climacteric, hot flush or flash, night sweat, vasomotor and a search filter for RCTs (Appendix S1). There was no language restriction.

**Data extraction**

Two reviewers (W.W.L. and S.I.) independently assessed the studies using the pre-defined criteria
described above. Disagreement was resolved with discussion with the steering committee. Full articles were obtained and data were extracted using a pre-specified extraction sheet.

**Quality assessment**

Jadad scoring was used for assessing the methodological quality of the included trials \(^{15}\). The 5 point validated scoring system assesses the following, whether the trial: (1) was described as randomized (1 point); (2) used an appropriate method of randomization (1 point); (3) was blinded (1 point); (4) used an appropriate method of blinding (1 point); and (5) accounted for all patients randomized (1 point); \(\leq 2\) points was considered low quality, \(\geq 3\) was considered medium to high quality.

The quality of describing and reporting the outcome was assessed by using the 6-point Management of Otitis Media with Effusion in Cleft Palate (MOMENT) scoring criteria \(^{16}\), which has been used previously in the context of quality assessment of studies for the development of a core outcomes set and a cutoff of \(\geq 4\) to indicated a high quality trials. The following points were considered: whether the primary outcome was (1) clearly stated (1 point); (2) clearly defined (1 point); whether the secondary outcomes were (3) clearly stated (1 point); (4) clearly defined (1 point); (5) whether the authors explained the use of the outcomes they have selected (1 point); (6) whether specific methods were used to enhance the quality of outcome measurement (1 point).

**Patient involvement**

Patients were not involved in the stage of conducting the systematic review but they will be involved in the subsequent steps (Delphi and consensus meeting) of developing the core outcome set.

**Core Outcomes**

Core outcomes do not exist in this research field hence they were not used in the systematic search. Our aim is to develop and disseminate core outcomes of menopausal symptoms and this systematic review is the first step of the process.
Funding
This study was funded by an MRC postdoctoral fellowship (SI, MR/N015177/1), NHMRC Practitioner Fellowship (MH, APP 1058935) and an NHMRC Principal Research Fellowship (GDM, APP1121844). The funders were not involved in any stage of conducting this systematic review.

Results
The search identified 5,591 studies, of which 2,711 duplicates were removed. We screened 2,880 titles and abstracts and excluded 2,372 records which did not meet the inclusion criteria. 544 studies were read in full. Of these, 330 were excluded; 59 because they included fewer than 20 women per study arm and 54 were not an RCT; 126 did not clearly state a sample size calculation; 52 did not measure vasomotor symptoms as the primary outcome; 39 were secondary analysis. Following these exclusions, 214 RCT were included (Figure 1). Table S1 describes the 214 studies with a total of 22,682 participants. The studies were published between 1994 and 2018. More than one third of the trials (77/214, 36%) were conducted in US. The follow up period ranged from 4-52 weeks, with half the included studies following up participants for 12 weeks (108/214, 50%).

Reported outcomes
The included trials reported 31 different interventions for menopausal vasomotor symptoms, of which 68 (32%) included hormone therapies and the remaining 146 non-hormonal therapies; 46 of which were prescription therapies and 100 were non-prescription therapies. Among these interventions, 1) oestrogen and/or progestogen therapies (61/214, 29%) and 2) over the counter dietary or herbal supplements (68/214, 32%) were the most common interventions (Table 1).

Forty-nine primary outcomes were identified from 214 RCTs including n=22,682 women. Almost half (94/214, 44%) RCTs only included postmenopausal women, 12 % (26/214) only included women with a history of breast cancer, and 5% (12/214) included peri and postmenopausal...
women. Around one quarter of RCTs (56/214, 26%) included both surgical and naturally peri and postmenopausal women. We categorized the primary outcomes into four domains: (1) purely vasomotor related outcomes (183/214, 86%); (2) quality of life related outcomes (9/214, 4%); (3) composite outcomes (17/214, 8%) and (4) functional impact, specifically how bothersome, interfering and problematic vasomotor symptoms are; for this review we will refer to the latter category as 'interference' outcomes (5/214, 2.3%). The largest group was purely vasomotor related outcomes, comprising 33 individual outcomes. The second largest group was composite outcomes, all of which included vasomotor symptoms as one of the parameters. Nine trials assessed quality of life and 5 trials assessed interference as primary outcomes (Table 2).

Measurement Tools

Seven different measurement tool categories were used to measure purely vasomotor related outcomes. Most (158/214, 74%) included trials used diary records of vasomotor symptoms and 24.7% (53/214) used menopause-specific subscales. Of these subscales, the Kupperman Menopausal Index (25/57, 44%), Greene Climacteric Scale (15/57, 26%), and Menopause Rating Scale (MRS) (10/57, 18%) were the three most frequently used measurement tools. The Hot Flush Rating Scale (HFRS) measures how vasomotor symptoms interfere with daily routine and activities. The Hot Flush Related Daily Interference scales (HFRDIS) and the shortened Hot Flush Interference (HFI) scale, have been used to measure interference due to vasomotor symptoms but were not the primary outcome of eligible RCTs so were not included in the systematic review. However, they will still be used for the subsequent Delphi process. Other subjective vasomotor symptoms measurement tools included a 20-item structured symptom checklist; two of the items asking about the presence of hot flushes and cold/night sweats, a five point (from none to very severe) scoring system about the severity of hot flushes and night sweats, Interactive Voice Response System to record the number and severity of the hot flushes and self-reported surveys. Objective measures of vasomotor symptoms such as skin conductance were used in five trials in addition to subjective measures (Table 3).
Diaries were used for recording 25 different types of menopausal vasomotor related outcomes, and accounted for 57% (25/44) of all primary outcomes. The number, frequency, severity and intensity of menopausal vasomotor symptoms were the most commonly reported vasomotor related outcomes assessed by diaries. However, there was substantial variation in the definitions of each outcome. For example, for frequency, the majority of included studies (72/214) reported the “number of vasomotor symptoms per 24 hours” (8 retrospectively and 64 prospectively), and 39/214 measured the “number of vasomotor symptoms per week”. Table S2 shows the complete list of vasomotor related outcomes recorded by diaries and how often they have been reported in RCTs of intervention studies for vasomotor symptoms.

Quality of life outcomes were measured by three scales: Menopausal-Specific Quality of Life (MENQOL) 28, 77, 90, 98, 109, 122, 130, 141, 181, 197, 198, 228, Women’s Health Questionnaire (WHQ) 135, 163 and the European Organisation for Research and Treatment of Cancer Quality of Life-Care30 (EORTC QLQ-C30) 136. Of these, 14 out of 15 trials chose menopausal-specific scales (MENQOL, WHQ). Only one trial including women with vasomotor symptoms after breast cancer used a general QOL scale (EORTC QLQ-C30) 136 (Table 3).

Variation in the definitions of vasomotor related outcomes

There was substantial heterogeneity in the definition of vasomotor related outcomes. Three different definitions were used to measure the frequency of vasomotor symptoms. Most studies (79/97, 81%) defined frequency as the number of hot flushes or night sweats, whereas 18 studies did not define how frequency was measured. The severity of vasomotor symptoms was defined in nine different ways and the intensity in seven different ways (table S3). The 68 studies reporting composite outcomes for vasomotor symptoms utilized 11 different ways of defining the composite score. The most commonly used approach (27/68, 40%) measured the number of hot flushes and
night sweats and calculated a composite score weighted by severity rating. There was considerable overlap between composite score definitions.

Quality assessment of trials

Regarding methodological quality, 34% (73/214) of included RCTs scored 5 out of 5 points on the Jadad scale. More than half of the trials (118/214, 55%) scored 6 out of 6 points on the MOMENT scale (Table S1).

Discussion

Main Findings

This is the first systematic review of outcomes used to measure vasomotor symptoms in randomized controlled trials of interventions. Our findings demonstrate major inconsistencies in how treatments for the same symptoms have been evaluated. For example, the severity of hot flushes and night sweats had nine different definitions. Overall, the most commonly used outcomes for vasomotor symptoms (based on 214 RCT including 22,682 women) were the frequency and intensity of vasomotor symptoms or a compound measure of these (n=59). A smaller number of studies (n=5) took a different approach and measured the interference due to vasomotor symptoms. It remains unclear which measures of vasomotor symptoms best reflect the priorities of patients, clinicians and researchers and this will be addressed by the development of a Core Outcome Set. Inclusion of the Core Outcome Set in future intervention studies for vasomotor symptoms will enhance the quality and relevance of trials and facilitate decision making by clinicians and patients.

Strengths and limitations

We conducted a comprehensive search strategy with a robust methodological design to include all large (>20 participants per arm) RCTs of interventions for vasomotor symptoms. Two researchers
independently evaluated the available evidence to minimize overlooking relevant evidence. To our knowledge, this is the first time that reported vasomotor related outcomes have been synthesized, a necessary step to inform the Delphi process for key stakeholders to rate the components of the core outcome set\textsuperscript{12}. Whilst most included trials were of medium or high methodological standard the diverse nature of the outcome measures used diminishes the value of these trials to inform patient choices and clinical decision making.

This study focused on menopausal vasomotor symptoms in the first instance. We recognize that personal, ethnic, cultural and geographical factors influence the nature and experience of menopause and that not all women experience vasomotor symptoms at menopause \textsuperscript{235}. We comprehensively searched three major databases and it is unlikely we have missed an RCT published elsewhere. We acknowledge we did not search CINAHL but we doubt that additional RCTs could only be identified in this database. We included randomized trials with vasomotor related symptoms as a primary outcome with over 20 participants in each arm, excluding observational studies and pilot studies. However, given the large number of included studies, we do not anticipate that we have missed outcomes not captured in larger trials. We recognize that this systematic review was limited to trials where vasomotor symptoms were the primary outcome. However, given the large number of studies included, we do not anticipate having missed important outcomes. The expert panel and Delphi process will highlight any additional important outcomes that may have been overlooked because they were not included in treatment studies or were reported as secondary outcomes. We also appreciate that our findings may be skewed towards FDA driven outcomes since many studies were conducted in US. We have only listed the range of outcome measures used and have not applied any qualitative assessment of the value or importance of these measures for women or clinicians. Only a few relatively recent RCTs have measured the impact of interventions on the interference caused to women by vasomotor symptoms and it is uncertain whether the frequency/severity or interference of symptoms best reflects women’s treatment priorities. These issues will be addressed by the Delphi survey and the subsequent consensus meeting. Most published RCTs of interventions for vasomotor symptoms focused on Caucasian women who may experience menopause differently from other
ethnicities. The COMMA consortium includes representation from a wide range of geographical areas and ethnic groups to ensure that the Core Outcome Set reflects variations in stakeholder priorities.

**Interpretation**

Inconsistency in measures used for the evaluation of treatments for vasomotor symptoms limits comparisons between treatments and the interpretation of findings for clinical practice. Understanding the efficacy of new treatments and how they compare to existing approaches requires the use of standardized outcome measures that are meaningful to patients and feasible for clinicians and researchers.

A Core Outcome Set does not preclude the inclusion of additional outcome measures, but sets a minimum standard of outcomes that should be reported in all interventional trials. This systematic review is the first step towards development of meaningful consensus by identifying how vasomotor symptoms have been measured to inform consensus through the Delphi process.

**Conclusion**

Most intervention studies for vasomotor symptoms have measured either frequency or severity of symptoms, or a combination of both. Some have measured the interference caused to daily life due to symptoms. There is a need for consensus around the optimum outcomes and how these should be measured to facilitate comparisons between interventions and ensure patient centered clinical practice.

**Disclosure of interest:** No conflict of interest to disclose. Completed disclosure of interest forms are available to view online as supporting information.

**Contribution of authorship:** MH and SI conceived the idea and set the protocol. GM, RN and
MAL refined the protocol. SI and WW conducted the systematic search and SI wrote the first draft of the paper with contribution from WW in writing the methods. MSH provided useful insight regarding the bothersome aspect of menopausal symptoms. All authors edited and accepted the manuscript prior to submission.

**Ethics approval:** No ethics approval was required as we have summarised already published data.

**Funding:** This study was funded by an MRC postdoctoral fellowship (SI, MR/N015177/1), NHMRC Practitioner Fellowship (MH, APP 1058935) and an NHMRC Principal Research Fellowship (GDM, APP1121844). The funders were not involved in any stage of conducting this systematic review.
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Legends

Figure 1. Flowchart of search strategy.
Table 1. Interventions for menopausal vasomotor symptoms

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Trials, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone therapy</strong></td>
<td>68 (32)</td>
</tr>
<tr>
<td>Oestrogen alone</td>
<td>45</td>
</tr>
<tr>
<td>Oestrogen+progestogen</td>
<td>12</td>
</tr>
<tr>
<td>Oestrogen+bazedoxifene</td>
<td>1</td>
</tr>
<tr>
<td>Progestogen alone</td>
<td>4</td>
</tr>
<tr>
<td>Tibolone</td>
<td>6</td>
</tr>
<tr>
<td><strong>Nonhormonal therapy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Prescription therapies</strong></td>
<td>46 (21)</td>
</tr>
<tr>
<td>SSRIs/SNRIs</td>
<td>26</td>
</tr>
<tr>
<td>Antiepileptic</td>
<td>10</td>
</tr>
<tr>
<td>ERr 731</td>
<td>2</td>
</tr>
<tr>
<td>BRN-01</td>
<td>1</td>
</tr>
<tr>
<td>Cinnarizin</td>
<td>1</td>
</tr>
<tr>
<td>Gamolenic acid</td>
<td>1</td>
</tr>
<tr>
<td>L-isoleucine</td>
<td>1</td>
</tr>
<tr>
<td>MF 101</td>
<td>1</td>
</tr>
<tr>
<td>Neurokinin 3</td>
<td>1</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>1</td>
</tr>
<tr>
<td>RAD 1901</td>
<td>1</td>
</tr>
</tbody>
</table>
**Nonprescription therapies**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over the counter dietary and/or herbal products</td>
<td>68</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>5</td>
</tr>
<tr>
<td>Exercise</td>
<td>4</td>
</tr>
<tr>
<td>Lifestyle education</td>
<td>3</td>
</tr>
<tr>
<td>Relaxation</td>
<td>3</td>
</tr>
<tr>
<td>Paced respiration</td>
<td>4</td>
</tr>
<tr>
<td>Cognitive therapy/Cognitive behavior therapy</td>
<td>2</td>
</tr>
<tr>
<td>Mindfulness training</td>
<td>1</td>
</tr>
<tr>
<td>Guasha</td>
<td>1</td>
</tr>
<tr>
<td>Local thermal therapy</td>
<td>1</td>
</tr>
</tbody>
</table>

**Clinical hypnosis**

**Total RCTs**

| Abbreviations: Randomised controlled trials (RCTs), Selective serotonin reuptake inhibitors (SSRIs), Serotonin and norepinephrine reuptake inhibitors (SNRIs), Menopausal Formula 101 (MF 101) |
| Err 731: A special extract from the roots of Rheum rhaponticum, referred to as ERr 731 (trade name Phytoestrol N) |
| BRN-01: A homeopathic medicine registered in France for menopausal hot flushes, combining the five homeopathic medications: Actaea racemosa (4 centesimal dilutions [4CH]), Arnica montana (4CH), Glonoinum (4CH), Lachesis mutus (5CH), and Sanguinaria canadensis (4CH). |
| RAD1901: An orally available, selective oestrogen receptordegrader (SERD) and selective oestrogen receptor modulator (SERM) |
Table 2. Vasomotor related outcome categories

<table>
<thead>
<tr>
<th>Outcome categories</th>
<th>The number of ways the outcomes is expressed (n)</th>
<th>Trials, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purely Vasomotor symptoms</td>
<td>33</td>
<td>177 (83)</td>
</tr>
<tr>
<td>Frequency of HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of HF/NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of moderate to severe HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of moderate to severe HF/NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of HF/NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of moderate to severe HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of severe HF/NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of HF</td>
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<tr>
<td>Severity of HF/NS</td>
<td></td>
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<tr>
<td>Severity of moderate to severe HF</td>
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<td></td>
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<tr>
<td>Severity of moderate to severe HF/NS</td>
<td></td>
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<tr>
<td>Intensity of HF</td>
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<td></td>
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<tr>
<td>Intensity of HF/NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of HF</td>
<td></td>
<td></td>
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<tr>
<td>HF (composite/severity) score</td>
<td></td>
<td></td>
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<tr>
<td>41% reduction in HF</td>
<td></td>
<td></td>
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<tr>
<td>44% reduction in HF</td>
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<tr>
<td>50% reduction in HF</td>
<td></td>
<td></td>
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<tr>
<td>75% reduction in HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of awakenings resulting from nocturnal vasomotor symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 50% patients halved the distress of HF/NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe rate of HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of HF reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients responding about vasomotor symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasomotor complaints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage change in HF score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasomotor symptoms (assessed with the Blatt-Kupperman Index)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF (assessed with the Greene climacteric)</td>
<td></td>
<td></td>
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<tr>
<td>Sweating at night assessed with the Greene climacteric</td>
<td></td>
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</tr>
<tr>
<td>Vasomotor symptoms per day (HF and NS, assessed with the Wiklund scale)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasomotor symptom intensity (assessed with the Wiklund scale)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Simplified Menopausal Index score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quality of life (QOL)</strong></td>
<td>4</td>
<td>9 (4)</td>
</tr>
<tr>
<td><strong>Interference</strong></td>
<td>5</td>
<td>11(5)</td>
</tr>
<tr>
<td>The extent HF/NS regarded as problem during last week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How distressed one feels about HF during last week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much HF interfered with daily routine over the last week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bothersomeness of HF/NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived Perimenopausal disturbances scale score</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Composite</strong></td>
<td>7</td>
<td>17 (8)</td>
</tr>
<tr>
<td>VMS+ QOL</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>VMS + urogenital symptoms</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>VMS + sleep quality</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>VMS + side-effect</td>
<td>3</td>
<td></td>
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<tr>
<td>VMS + endocrine symptoms</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>VMS + pharmacodynamic markers</td>
<td>1</td>
<td></td>
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<tr>
<td>VMS + QOL + satisfaction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total RCTs</strong></td>
<td></td>
<td>214</td>
</tr>
</tbody>
</table>

Abbreviations: Hot flushes (HF), night sweats (NS), vasomotor symptoms (VMS), quality of life (QoL)
Table 3. Tools for measuring vasomotor related outcomes

<table>
<thead>
<tr>
<th>Tools</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td><strong>Purely vasomotor symptoms</strong></td>
<td></td>
</tr>
<tr>
<td><em>Hot flushes diary/electronic diary</em></td>
<td>158</td>
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<tr>
<td><em>Menopausal-specific scale</em></td>
<td>53</td>
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<tr>
<td>Kupperman Menopausal Index (KMI)</td>
<td>25</td>
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<tr>
<td>Greene Climacteric Scale (GCS)</td>
<td>15</td>
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<tr>
<td>Menopause Rating Scale (MRS)</td>
<td>10</td>
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<tr>
<td>Wiklund Vasomotor Symptom Subscale score</td>
<td>1</td>
</tr>
<tr>
<td>Perceived Perimenopausal Disturbances Scale</td>
<td>1</td>
</tr>
<tr>
<td>Simplified Menopausal Index (SMI)</td>
<td>1</td>
</tr>
<tr>
<td><em>Structured menopausal-specific Checklist</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Skin conductance monitor system</em></td>
<td>1</td>
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<tr>
<td><em>Interactive voice system</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Symptoms scoring system</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Self-reported validated survey instruments</em></td>
<td>1</td>
</tr>
<tr>
<td><strong>Quality of life</strong></td>
<td>15</td>
</tr>
<tr>
<td>MENQOL</td>
<td>12</td>
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<tr>
<td>WHQ</td>
<td>2</td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>1</td>
</tr>
<tr>
<td><strong>Interference</strong></td>
<td></td>
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<tr>
<td>The Hot Flush Rating Scale (HFRS)</td>
<td>5</td>
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</table>
Records identified through database search n=5,591
  CENTRAL: 1676
  EMBASE: 2236
  MEDLINE: 1679

Duplicates removed n=2,711

Records screened (titles and abstracts) n=2,880

Records excluded n=2,372

Records screened (full text) n=544

Excluded studies n=330
  ≤20 participants per arm n=59
  Not RCT n=54
  No sample size calculation n=126
  VMS not primary outcome n=52
  Secondary analysis: n=39

Studies included n=214