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Title: Vasomotor symptoms due to natural menopause; systematic review and network meta-analysis (NMA) of treatment effects from the NICE Menopause Guideline

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Running head: Network meta-analysis of vasomotor symptoms in menopause

Abstract

Background: Vasomotor symptoms (VMS) are the hallmarks of menopause, occurring in approximately 75% of postmenopausal women in the UK and are severe in 25%.

Objectives: To identify which treatments are most clinically effective for the relief of VMS for non-hysterectomized women in natural menopause.

Search Strategy: English publications in MEDLINE, Embase and The Cochrane Library up to 13th January 2015 were searched.

Selection Criteria: Randomized trials (RCTs) of treatments for women with a uterus for the outcomes of frequency of VMS (up to 26 weeks), vaginal bleeding and discontinuation.

Data Collection and Analysis: Bayesian network meta-analysis (NMA) using mean ratios (MRs) and odd ratios (ORs).

Main Results: Across the three networks, 47 RCTs of 16 treatment classes (N=8326 women) were included. When compared to placebo, transdermal oestradiol and progestogen (O+P) had the highest probability of being the most effective treatment for VMS relief (69.8%) (MR: 0.23 [95%CrI (0.09, 0.57)] whereas oral O+P was ranked lower than transdermal O+P, although oral and transdermal O+P were no different for this outcome (MR: 2.23 [95%CrI (0.7, 7.1)]. Isoflavones and black cohosh were more effective than placebo, though not significantly better than O+P. Not only were SSRIs or SNRIs found ineffective in relieving VMS but they also had significantly higher odds of discontinuation than placebo. Limited data were available for bleeding therefore no conclusions could be made.

Conclusions: For non-hysterectomized women, transdermal O+P was the most effective treatment for VMS relief.

Keywords: menopause, uterus, network meta-analysis, hormonal treatment.

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42 **Tweetable abstract:** Which treatment best relieves menopause flushes? Results from the #NICE

43 guideline network meta-analysis

Introduction

Menopausal symptoms are extremely common. Vasomotor symptoms (VMS) comprising hot flushes and night sweats are the most common menopausal symptoms occurring in approximately 75% of postmenopausal women, with 25% of these being severely affected in the UK[1]. The duration and severity of menopausal symptoms experienced are not uniform – symptoms may develop in the years before the final menstrual period and may persist for a few years or for many years in postmenopause.

Hot flushes often begin as the sudden sensation of heat centred on the upper chest and face. In some instances, this will become generalised, lasting for several minutes, and can be associated with profuse perspiration, palpitations or anxiety which may be very distressing and limit activities of daily living, particularly when they occur repeatedly during the day and at night. At night, hot flushes and night sweats will often cause insomnia that leads to fatigue. The mechanism of VMS appears to involve the central nervous system, possibly due to narrowing of the thermoregulatory-neutral zone in women with hot flushes, associated with instability of the skin blood vessels[2].

Different treatment options, pharmacological and non-pharmacological, have been used by women to relieve the VMS during menopause. Some of these treatments, such as hormone replacement therapy (HRT) target a “replacement” of oestrogen levels HRT comprises synthetic hormones including oestradiol, conjugated equine oestrogens, oestradiol valerate and several synthetic progestogens as well as tibolone which exhibits estrogenic, progestogenic and androgenic effects. Other treatments, such as herbal medicines and psychological therapies may work in different ways. As VMS may resolve naturally, some women simply do not wish to take hormones, while for others HRT is contraindicated, for example women who have (or are at high risk of) hormone-dependent cancer.

We aim to present the evidence obtained via a systematic review (SR), using network meta-analysis (NMA), of pharmacological and non-pharmacological treatments for the relief of VMS, relief of adverse events (such as vaginal bleeding)and discontinuation. This NMA formed part of the evidence underpinned the development of National Institute of Health and Care Excellence (NICE) Menopause Guideline (NG23) (https://www.nice.org.uk/guidance/ng23)[3]. The use of NMA is recommended in healthcare decision making when multiple treatments are considered for one indication and these treatments have not been directly compared in the same trials.

Methods

Systematic Reviews

The protocol of the SR was agreed by the Guideline Development Group (GDG) (Appendix S1), was conducted as part of the development of NICE guideline on menopause (NG23) https://www.nice.org.uk/guidance/ng23 and is reported according to the PRISMA extension statement for systematic reviews incorporating NMAs of health care interventions[4].. A cost-effectiveness model using results from this NMA, in addition to other evidence, were used by the GDG to make recommendations in the guideline. In summary, the SRs included only randomised controlled trials (RCTs) that assessed pharmacological and/or non-pharmacological treatments for reducing the frequency of VMS, treatment discontinuation and vaginal bleeding for women aged 45 years or older with a diagnosis of natural menopause (defined as amenorrhea for at least 12 consecutive months).

The population in the NMA protocol was stratified into three groups that formed three networks of connected treatments: women with a uterus, women without a uterus, women with a history or at risk of breast cancer. This paper presents the results of the first network (women with a uterus). For non-oestrogenic treatments we included studies of women without a uterus as their effect was found to be clinically similar. For studies investigating oestrogen plus progestogen we included

mixed studies of women with a uterus and without a uterus as long as more than two thirds (66.6%) of the study sample were women with a uterus (Appendix S1).

The efficacy endpoint was the frequency of VMS at the end of treatment, whereas vaginal bleeding and treatment discontinuation were considered measures of adverse events. Although distress caused by VMS may have been an equal relevant outcome for women in menopause, the frequency of VMS was the most commonly reported outcome in studies, and the Guideline Committee highlighted that VMS were highly prevalent among women seeking treatment for menopausal symptoms. Vaginal bleeding and treatment discontinuation were prioritised due to their importance on continuity of healthcare, costs of further treatment, and long-term impact. .

The time points of outcomes recorded were guided by clinical decision on the minimum duration of a trial for the intervention to be effective. Non-hormonal treatments were considered by the GDG to take a minimum of four weeks to be effective, whilst hormonal treatments were considered to take longer (12 weeks). As shorter-term outcomes were the focus of this review, 26 weeks was considered to be the maximum follow-up time we would include, to avoid long-term changes in treatment efficacy that might cause heterogeneity within the network.

All searches were conducted in MEDLINE Embase and The Cochrane Library up to 13th January 2015 restricted to English written articles according to the parameters stipulated within the NICE Guidelines Manual 2015 (https://www.nice.org.uk/article/PMG20/chapter/4-Developing-review-questions-and-planning-the-evidence-review) (Appendix S2),. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Full search strategies were published as part of the full NICE guideline (http://www.nice.org.uk/guidance/ng23/evidence/appendices-ag-559549262).

Search strategies were quality assured by cross-checking reference lists of highly relevant papers and comparing with search strategies in other SRs.

Data extraction

Data were double extracted in a structured form using a guide developed by the authors for Data Extraction for Complex Meta-anALysis (DECiMAL) independently by two reviewers[55]. Discrepancies in data extraction were addressed by a senior reviewer who resolved any conflicts.

The quality of the studies was evaluated using two domains (risk of bias, indirectness) of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/)[6]. Detailed results for risk of bias domains are shown in Table S2.

Statistical models

NMA was formulated to synthesise direct and indirect evidence of treatments' effects to reduce the frequency of VMS, treatment discontinuation and vaginal bleeding using the software WinBUGS version 1.4.3. We used statistical models for both fixed and random effects that allowed inclusion of multi-arm trials and accounted for the correlation between arms in the trials with any number of trial arms[7]. A class effect model was selected for the NMA with the underlying assumption that the effectiveness of different treatments under the same class would be comparable. This decision was made to maximise the availability of data and borrow strength from different trials. Data were available on dosing for many treatments, but the sparseness of the networks meant that it was necessary to borrow strength on dosing within treatments by assuming different doses of the same treatment had the same class effects (fixed effects model (FE)). A model allowing for within-class variability was also assessed to check if it improved model fit and reduced heterogeneity (random effects model (RE)). Two RE models for this were explored: an exchangeable dose effects model, where the pooled relative effects of different treatment doses were assumed to be randomly distributed within each treatment with a common variance (requiring modelling using a second variance parameter); and a fixed dose effects model, where the pooled relative dose effects are assumed equal for all doses of a treatment. For treatments where dosing information was not

available, the relative effect at the dose level was assumed to be equal to the treatment effect in both models.

WinBUGS code was adapted from the Dias et al 2011 and is available from the NICE appendices (https://www.nice.org.uk/guidance/ng23/evidence/appendices-ik-559549264). The following prior distributions were used:

- Log mean ratios (MRs) in the comparator arms for each study were normally distributed with mean of zero and variance of 1000
- Pooled log MRs at the treatment or class level (depending on model used) were normally distributed with mean of zero and variance of 1000
- Between-study standard deviation followed a uniform distribution between zero and two
- Within-class standard deviation followed a uniform distribution between zero and two

Placebo was selected as the baseline comparator for all networks as it was the treatment arm most commonly evaluated in RCTs. As no dependency on time was identified in exploratory analyses, discontinuation of treatment and vaginal bleeding were treated as dichotomous outcomes and were modelled on the log-odds ratio scale (Figure S2). Exploratory analyses also showed that baseline frequency of VMS followed an overdispersed Poisson distribution thus it was not appropriate to use a standard Poisson distribution to model the frequency of VMS (Figure S3). The negative binomial distribution can be used to model an overdispersed Poisson distribution, by including a parameter that accounts for the overdispersion[8,9,10]. The mean of this negative binomial is interpreted as the rate of the over-dispersed Poisson and can be approximated by a normal distribution. We therefore model the mean using a log link function and relative treatment effects are estimated as log-mean ratios. Our motivation was to model data as closely as possible to the mechanism by which they were generated (i.e. from an overdispersed Poisson distribution) and this approximation provided a

simple computational solution whilst retaining the interpretation of the pooled effect as mean rates of VMS

On the log mean ratio scale, final and change from baseline frequencies of VMS could not be pooled, so the latter was transformed so that all effects could be modelled as final frequencies. A correlation coefficient of 0.55 was used to estimate final frequencies from change from baseline This was calculated from two included studies which reported baseline, final and change from baseline results in full[11,12].

All three models (FE, RE with fixed dose effects, RE with exchangeable dose effects) were compared based on residual deviance and deviance information criteria (DIC)[7,13]. Between-studies heterogeneity estimates from random effects models are presented as median and 95% credible intervals (95%CrI).

Inconsistency in the networks was tested in closed loops of treatment comparisons by node-splitting[14]. This technique allows the splitting of direct and indirect information contributing to each treatment effect. The difference between these contributions can be statistically tested, with a rejection of the null hypothesis indicating significant inconsistency in the network.

The output of the NMA was expressed as the probability of each treatment being the best for an outcome (based on the proportion of Markov chain simulations in which a treatment ranked first) and the ranking of treatments (presented as median rank and its 95%CrI). The estimation of summary estimates (mean ratios [MRs] or odds ratios [ORs]) were also calculated for comparisons of the direct and indirect evidence using medians and 95%CrIs from the posterior distributions.

Two types of sensitivity analyses were predefined in the NMA protocol. The first focused on changing the value of the correlation coefficient used to estimate final frequencies of VMS from change from baseline, from 0.55 in the original analysis to a typically assumed correlation between baseline and follow-up of 0.75. The second analysis tested if differences in treatment efficacy could

be explained by differences in dosing. Studies investigating the treatment of low dose oral oestradiol plus progestogen were removed from the analysis to determine if this dose was reducing the overall efficacy of oral oestradiol plus progestogen in the model. The final results were not found to be sensitive to either of these changes.

A further post-hoc sensitivity analysis was considered to investigate the effect of including mixed population studies (women with and without a uterus) of oestrogen plus progestogen. However, as there was only a single study[32] that included mixed populations for this treatment comparison, exclusion of the study removed oestrogen plus progestogen oral from the network and prevented estimation of the efficacy of this treatment. No other results were affected by the exclusion of this study.

Results

47 RCTs matched the protocol, presented information for at least one of the outcomes and were included in the NMA (Figure S1). For the two first networks (frequency of VMS and discontinuation of treatment), DIC suggested that there was a small difference between any of the models (differences less than 5 points are not considered meaningful) (Tables S7). However, the residual deviance for the random effects model with fixed dose effects for both these networks was slightly closer to the number of unconstrained data points than either of the other models (for the fixed effects and random effects with exchangeable dose effects respectively). Therefore, the results of the random effects model with fixed dose effects are presented for these two networks. For the network of vaginal bleeding, the results of the fixed effects model are presented, as the estimate of heterogeneity for the random effects model was unstable, and strongly influenced by the prior distribution.

a. Reducing the frequency of VMS

A total of 32 RCTs of 12 treatment classes (placebo, sham acupuncture, oestrogen plus progestogen non-oral, oestrogen plus progestogen oral, tibolone, raloxifene, SSRIs/SNRIs, isoflavones, Chinese herbal medicine, black cohosh, multibotanicals, acupuncture) with a sample size of 4165 women were included for the NMA for VMS (Figure 1, Table S1). Two included RCTs was at very high risk of bias and 13 were high risk (Table S2). The other 21 RCTs were low or moderate risk. The combination of oestrogen plus progestogen via patches was found to be better than placebo (MR 0.23 95%CrI (0.09, 0.57)) at relieving VMS for women in menopause and had the highest probability of being the best treatment (68.9%) (Figure 2A, Table 1). Although, the 95%CrI for combination of oral oestrogen plus progesterone compared to placebo was wide (MR 0.52 (0.25, 1.06)), the point estimate suggested that it may have good efficacy, similar to that of transdermal oestrogen plus progestogen. In addition, there was strong evidence to suggest that the combination of oestrogen plus progestogen via patches was more effective than raloxifene, SSRIs/SNRIs, isoflavones and Chinese herbal medicine in relieving VMS. Isoflavones and black cohosh were also found to be better than placebo. There was no strong evidence of any other effects among other interventions in the network (Table S3).

High heterogeneity was found between studies, reducing the precision of estimates. This is likely to have arisen because of the clinical differences in patients included in the studies – the baseline frequency of hot flushes varied considerably between studies. Inconsistency was assessed in the closed loop between placebo, sham acupuncture and acupuncture, but no difference was found between results obtained through direct and indirect evidence (Table S3).

a. Treatment discontinuation

A total of 21 RCTs of 10 treatment classes (placebo, oestrogen plus progestogen oral, conjugated oestrogens plus bazedoxifene, tibolone, SSRIs/SNRIs, gabapentin, isoflavones, Chinese herbal medicine, multibotanicals, valerian root) with a sample size of 4829 women were included in the

network for discontinuation of treatment (Figure 1, Table S1). Because of high heterogeneity between the studies included in the NMA, uncertainty of the results was increased. Inconsistency could not be assessed in this network as there were no closed-treatment loops. Only 4 RCTs were at high risk of bias. The other 17 were low or moderate risk (Table S2). There was evidence that the combination of non-oral oestrogen plus progestogen had significantly lower odds of discontinuation than than placebo (OR 0.61 95%CrI (0.37, 0.99). In addition, there was evidence that conjugated oestrogens plus bazedoxifene (OR 0.31 95%CrI (0.1, 1.00)) was more effective than placebo in this outcome, although there was considerable uncertainty in this result. There was strong evidence that SSRIs/SSNIs were worse than placebo (OR 1.66 95%CrI (1.07, 2.61)) on discontinuation of treatment. There was evidence that Tibolone and SSRIs/SNRIs were worse than non-oral oestrogen plus progestogen and conjugated oestrogens plus bazedoxifene for this outcome (Figure 2B, Table 2, Table S4).

In this analysis, conjugated oestrogens plus bazedoxifene and valerian root were found to have the highest probability (37.34% and 37% respectively) of being the best treatments in relation to discontinuation of treatment among interventions with duration up to 26 weeks, although note that these probabilities are small and below 50%

a. Vaginal bleeding

The network of vaginal bleeding included five RCTs of 5 treatment classes (placebo, oestrogen plus progestogen oral, tibolone, SSRIs/SNRIs, gabapentin) (Figure 1, Table S1) with a sample size of 1367 women. Neither heterogeneity nor inconsistency could be assessed in the network due to its sparseness. A fixed effects model was used and there were no closed-treatment loops. One study was at high risk of bias, one was low risk, and the other three were moderate risk (Table S2). The sparseness of data within the network meant that there was a high degree of uncertainty in estimates, and no conclusions could be drawn regarding effects of treatments on vaginal bleeding (adverse event) (Figure 2C, Table S5, Table S6).

Discussion

This paper summarizes the evidence included in three SRs and analysed in NMAs for the outcomes of relief of frequency of VMS, treatment discontinuation and vaginal bleeding among pharmacological and non-pharmacological treatments for women with a uterus who have undergone a natural menopause. To our knowledge, this is the first publication using this type of complex analysis in the research field of menopause.

Main findings

NMA results showed that for women with a uterus, the oestrogen plus progestogen transdermal patch was the most effective treatment to relieve the frequency of VMS, with a lower odds of discontinuation compared with all the other available treatments (hormonal, non-hormonal and non-pharmacological). There was evidence that oestrogen plus progestogen taken orally may be more effective to relieve VMS than placebo, but this did not rank as highly as transdermal oestrogen plus progestogen in the hierarchy of the best treatment options for this outcome. However, in the clinical setting both may be considered as options, depending on the individual's response to treatment. Although isoflavones and black cohosh, were also shown to be more effective than placebo in relief of VMS for women with a uterus, there was no evidence that their efficacy differed from combined oestrogen plus progestogen. However, these results should be interpreted with caution as there was a variety of herbal preparations used in different studies. SSRIs/SNRIs were not found to be effective in relieving VMS but were found to have higher odds of discontinuation compared to the other treatments, as would be expected due to the serious side effects profile of these treatments. However, the NMA demonstrated that women treated with non-oral oestradiol plus progestogen or with conjugated oestrogens plus bazedoxifene were less likely to discontinue treatment than if they were treated with placebo or tibolone.

No conclusive points could be made for the outcome of vaginal bleeding for women with a uterus given the limited data for this outcome and the lack of inclusion of several interventions in the network.

During the NICE guideline development, results of clinical efficacy from the NMA were incorporated into a probabilistic cost-effectiveness analysis that informed the decision-making of the Guideline Committee. The Committeeconcluded that women with a uterus should be offered the treatment of oestrogen and progestogen (HRT) for the relief of VMS, following an individualized approach and after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. Health professionals should not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for VMS alone and should explain to women that although there is some evidence that isoflavones or black cohosh may relieve VMS there are health concerns in relation to safety of multiple preparations and interactions with other medicines (https://www.nice.org.uk/guidance/ng23/)

Strengths and Limitations

This is the first NMA designed to include simultaneous comparison of randomized evidence aiming to reduce the frequency of VMS for women in menopause. Advanced statistical techniques were employed to make best use of available evidence. A novel NMA model which accounts for the nature of the VMS data, distributed as overdispersed Poisson, and incorporates class effects and transformation of change from baseline scores of outcomes, was developed to make use of as much relevant and available data as possible. We were therefore simultaneously able to compare several interventions of interest to women and policy makers that had not been compared previously in head-to-head trials.

Overall there were relatively few studies included in the networks compared to the number of treatment comparisons. This may have led to the within-class standard deviation parameter not being fully informed, which could explain the better fit of the fixed dose effect RE model compared

311 to the exchangeable dose effect RE model. A dose-response relationship might have been expected
312 in the data, but as the protocol specified that treatments had to be administered within selective
313 doses specified in the British National Formulary, the range of doses was often very small.
314 Furthermore, body weights and absorption can vary substantially between patients, and this is likely
315 to lead to as much (if not more) variation in bioavailability of treatment than the administered dose.

316 Several decisions were made at the protocol stage that impacted the selection of data included in
317 the networks and therefore the representativeness of all available evidence in this area. For
318 example, we included only English-published studies , which may have limited our evidence on some
319 treatments (e.g. Chinese herbal medicines), and publication bias was not easily assessed.
320 Furthermore, it was decided to examine the role of different treatments used to reduce the
321 frequency rather than the severity of VMS, which resulted in some treatments such as cognitive
322 behaviour therapy being excluded from the NMA. The selection of outcomes for inclusion in the
323 NMA was based on both their clinical importance and relevance to women in menopause.
324 Frequency of VMS, discontinuation and vaginal bleeding were prioritised for inclusion due to their
325 high prevalence and availability of evidence.

326 Assumptions were also made for the minimum duration of trials for inclusion in the NMA and the
327 minimum acceptable criteria for mixed population studies. These assumptions are commonly made
328 when a complex meta-analysis is designed and aim to increase the homogeneity and validity of
329 included data. However, this resulted in a number of studies being excluded from further analysis.
330 Some studies were also excluded because the data reported did not give an indication of variability
331 (no information on standard deviation or standard error of results). For the small minority of studies
332 that were excluded because they did not connect to the network, their results and whether they
333 would influence decision-making were further discussed with the GDG. This information was used as
334 supplementary evidence to facilitate the Group's discussion which recognised the importance of
335 these treatments in the management of some women with menopause, especially if they do not

wish to be treated with pharmacological treatments (such as HRT) and these options were highlighted in terms of provision of general advice and information.

Interpretation

This is the first NMA designed to include simultaneous comparison of randomized evidence from pharmacological and non-pharmacological treatments aiming to reduce the frequency of VMS for women in menopause. After taking into account the assumptions used for this NMA and the limitations of this approach, these results provided a comprehensive framework for decision making by combing direct and indirect evidence on treatments for the relief of VMS in menopause. Our reviewed literature did not identify any other similar type of analysis that could be used for our results comparison.

Conclusions

There is evidence that transdermal oestradiol plus progestogen greatly reduces the frequency of hot flushes in women with a uterus. Although there is some evidence of efficacy of oral oestrogen plus progestogen treatment, the health economic analysis and the GDG's expert opinion supported the use of both types of oestradiol plus progestogen's administration in clinical practice.

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Disclosure of interests

We declare the following interests based on NICE's policy on conflicts of interests (available at: www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/code-of-practicefor-declaring-and-managing-conflicts-of-interest.pdf). MAL has been remunerated for chairing NICE guideline development committees and is vice chair of the Women's Health Expert Advisory Group to the Medicines and Healthcare products Regulatory Agency (MHRA). SD is co-investigator on an MRC/Pfizer collaboration grant in which Pfizer part-fund a researcher (not SD). GS, HP and YG have no conflicts of interest to declare. ICMJE disclosure forms are available as online supporting information.

Contributions to authorship

GS has prepared the first draft of the publication and was responsible for revisions and ensuring overall integrity of the process. All co-authors (GS, HP, YG, SD, MAL) contributed to reviews and approved the final version of the manuscript.

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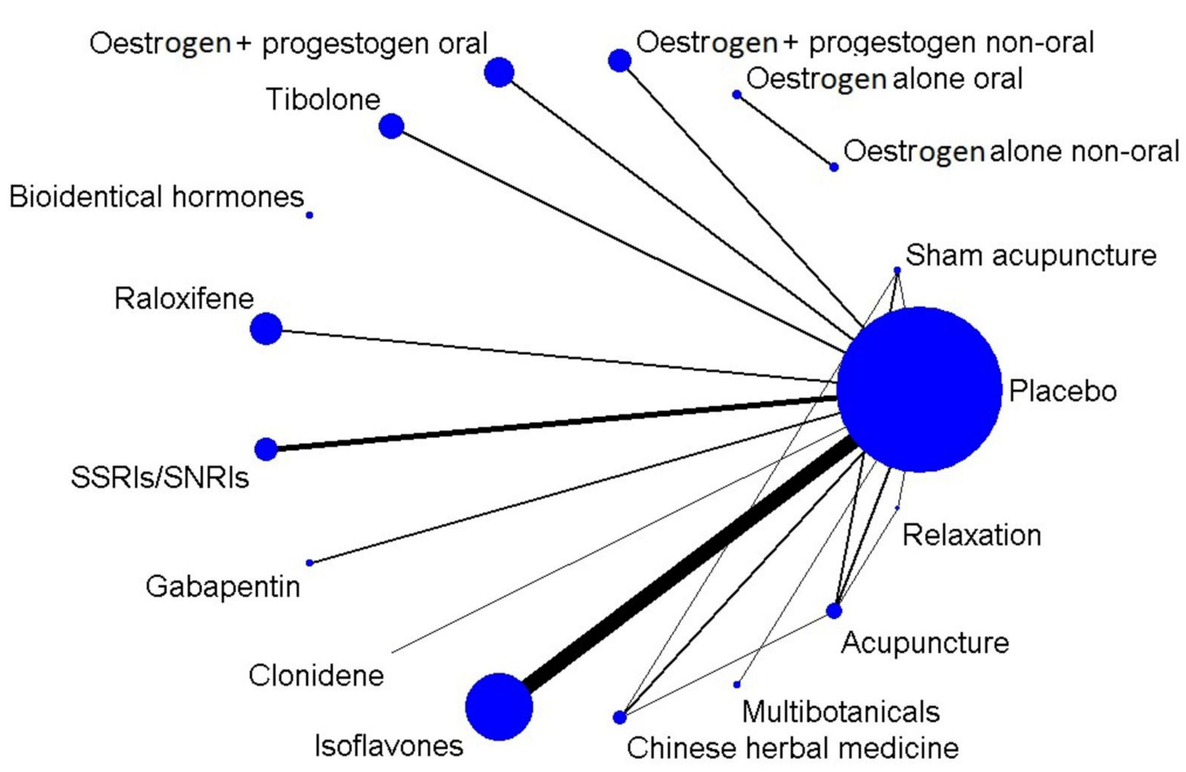
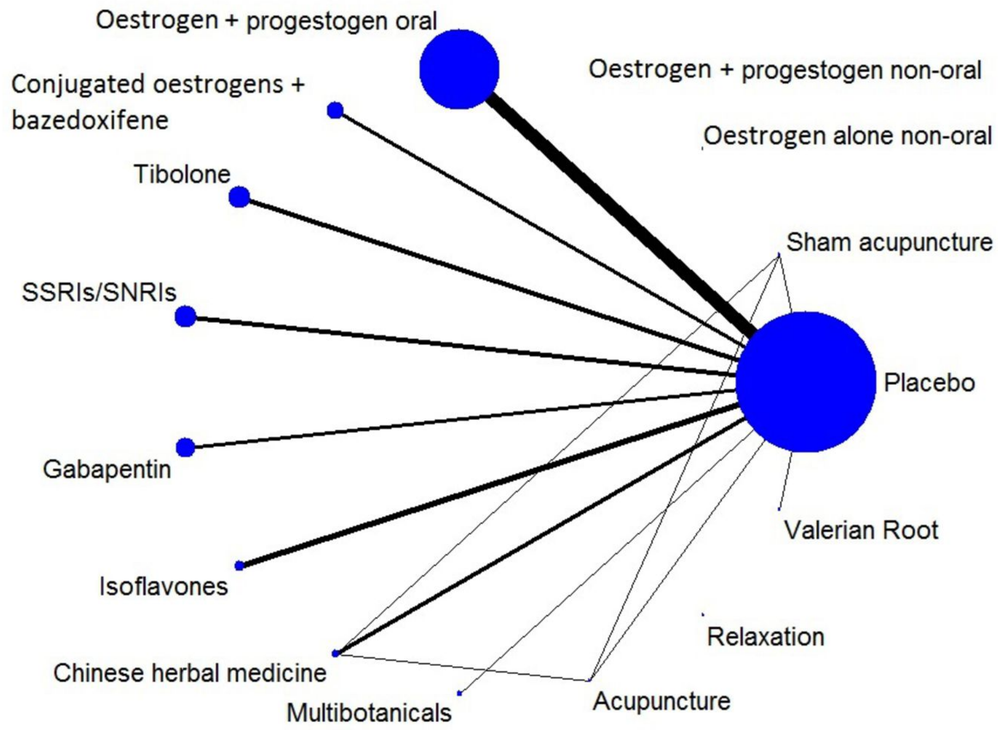
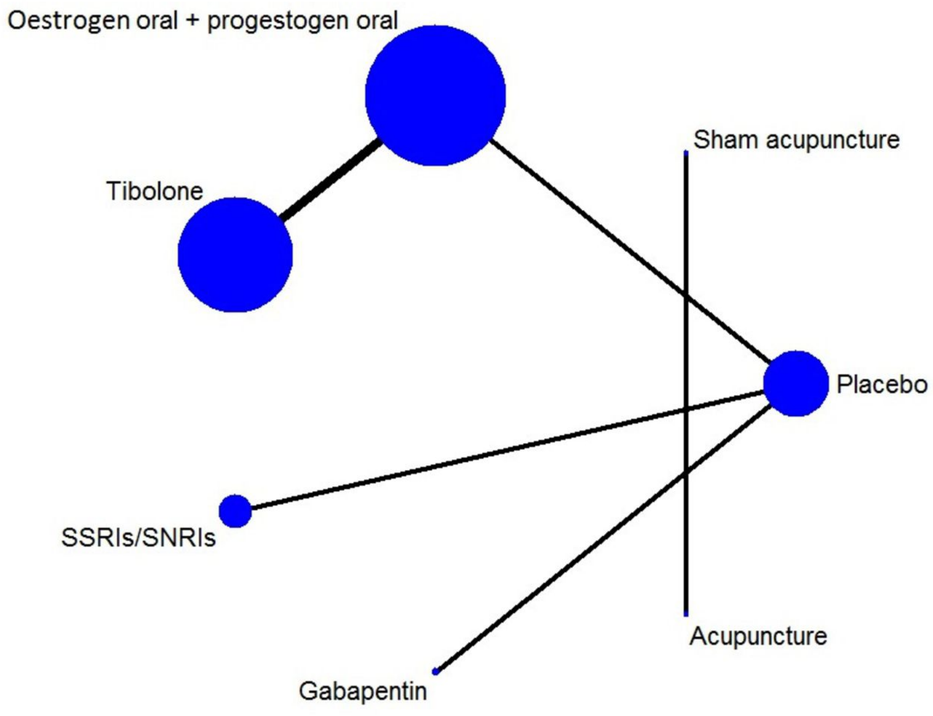
VMS - Women with a uterus



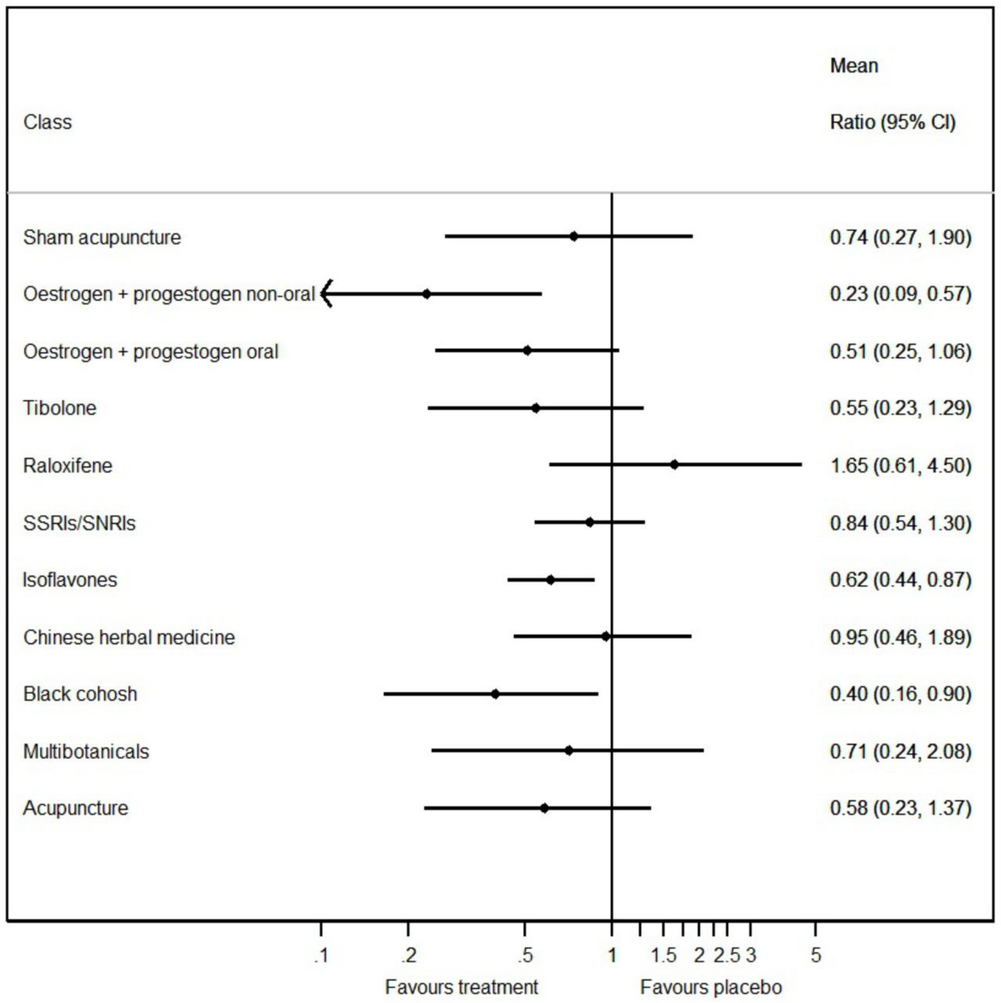
Discontinuation - Women with a uterus



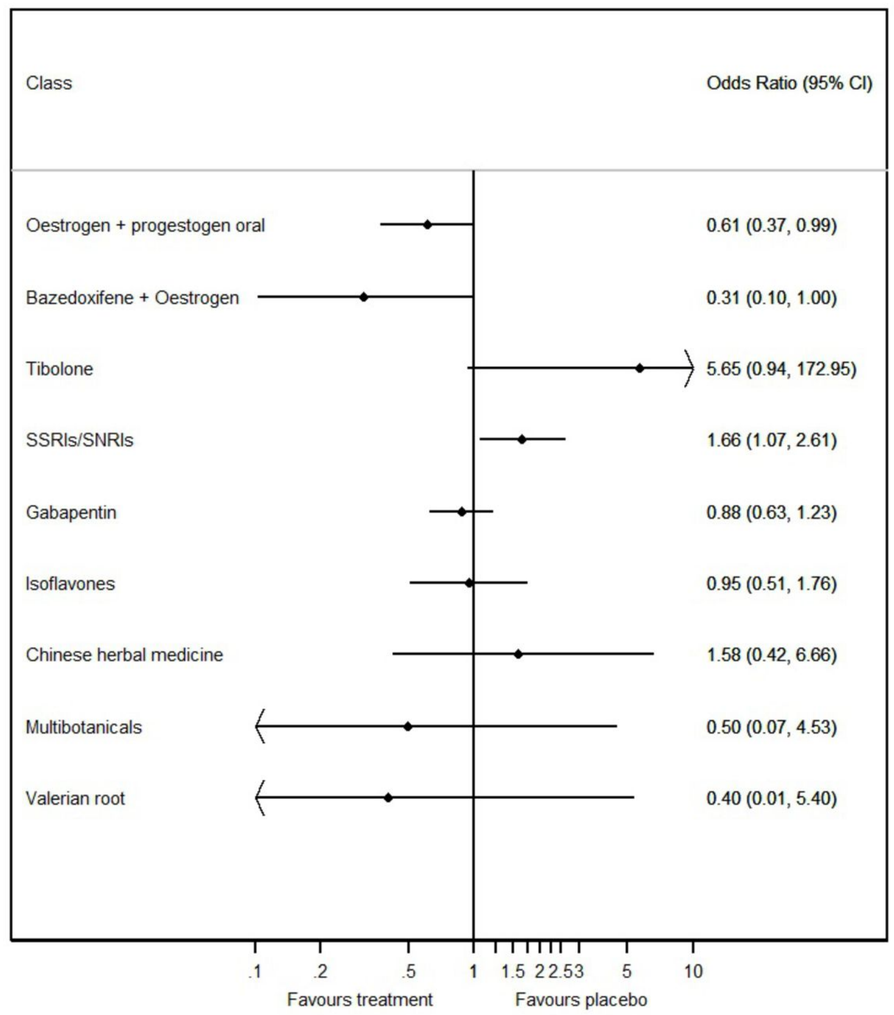
Vaginal Bleeding - Women with a uterus



A


Class
Mean
Ratio (95% CI)
Sham acupuncture
0.74 (0.27, 1.90)
Oestrogen + progestogen non-oral
0.23 (0.09, 0.57)
Oestrogen + progestogen oral
0.51 (0.25, 1.06)
Tibolone
0.55 (0.23, 1.29)
Raloxifene
1.65 (0.61, 4.50)
SSRIs/SNRIs
0.84 (0.54, 1.30)
Isoflavones
0.62 (0.44, 0.87)
Chinese herbal medicine
0.95 (0.46, 1.89)
Black cohosh
0.40 (0.16, 0.90)
Multibotanicals
0.71 (0.24, 2.08)
Acupuncture
0.58 (0.23, 1.37)
.1
.2
.5
1
1.5
2
2.5
3
5
Favours treatment
Favours placebo

B


Class
Odds Ratio (95% CI)
Oestrogen + progestogen oral
0.61 (0.37, 0.99)
Bazedoxifene + Oestrogen
0.31 (0.10, 1.00)
Tibolone
5.65 (0.94, 172.95)
SSRIs/SNRIs
1.66 (1.07, 2.61)
Gabapentin
0.88 (0.63, 1.23)
Isoflavones
0.95 (0.51, 1.76)
Chinese herbal medicine
1.58 (0.42, 6.66)
Multibotanicals
0.50 (0.07, 4.53)
Valerian root
0.40 (0.01, 5.40)
.1
.2
.5
1
1.5
2
2.5
3
5
10
Favours treatment
Favours placebo

C

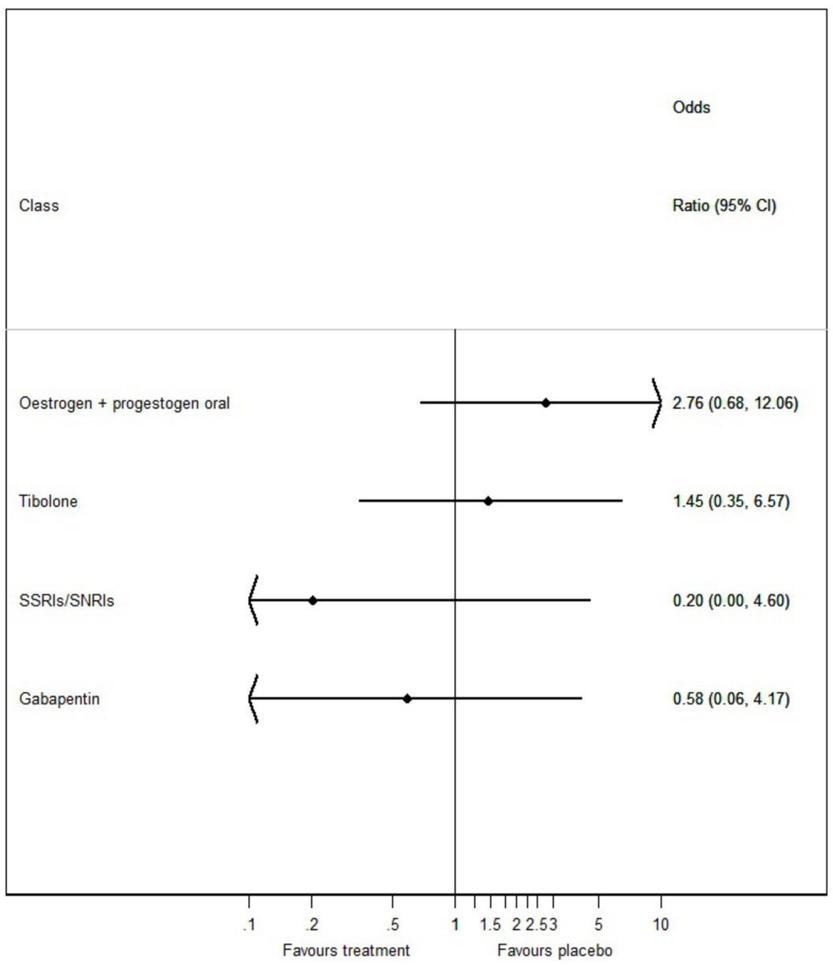

Class
Odds
Ratio (95% CI)
Oestrogen + progestogen oral
2.76 (0.68, 12.06)
Tibolone
1.45 (0.35, 6.57)
SSRIs/SNRIs
0.20 (0.00, 4.60)
Gabapentin
0.58 (0.06, 4.17)
.1
.2
.5
1
1.5
2
2.5
3
5
10
Favours treatment
Favours placebo

Table 1: Log mean ratios (with their 95% CI) of all interventions in the network and the probability of being the best treatment for reducing the frequency of VMS

	Median log mean ratios	95%CrI	Probability of being the best treatment	Median (95% CrI) treatment rank
Placebo	*Reference treatment*		0.00%	10 (7-12)
Sham acupuncture	-0.30	(-1.32, 0.64)	1.44%	7 (2-12)
Oestrogen + progestogen non-oral	-1.46	(-2.37, -0.56)	69.82%	1 (1-5)
Oestrogen + progestogen oral	-0.67	(-1.4, 0.06)	3.73%	4 (1-10)
Tibolone	-0.60	(-1.45, 0.25)	4.02%	5 (1-11)
Raloxifine	0.50	(-0.49, 1.51)	0.04%	12 (6-12)
SSRIs/SNRIs	-0.17	(-0.61, 0.26)	0.01%	8 (4-11)
Isoflavones	-0.48	(-0.82, -0.13)	0.10%	6 (3-9)
Chinese herbal medicine	-0.05	(-0.78, 0.63)	0.09%	9 (4-12)
Black cohosh	-0.92	(-1.8, -0.11)	14.23%	3 (1-9)
Multibotanicals	-0.34	(-1.43, 0.73)	2.88%	7 (1-12)
Acupuncture	-0.54	(-1.49, 0.31)	3.64%	5 (1-11)

Between-study heterogeneity: Standard deviation on the log MRs scale (SD) (95% CrI) 0.50 (0.37, 0.70)

Table 2: Log odd ratios (with their 95% CrI) of all interventions in the network and the probability of being the best treatment for discontinuation of treatment

	Median log odds ratios	95%CrI	Probability of being the best treatment	Median (95% CrI) treatment rank
Placebo	Reference treatment		0.00%	6 (4-8)
Oestrogen + progestogen oral	-0.50	(-0.99, -0.01)	2.83%	3 (1-6)
Conjugated oestrogens plus bazedoxifene	-1.16	(-2.28, 0.002)	37.34%	2 (1-6)
Tibolone	1.73	(-0.06, 5.15)	0.03%	10 (6-10)
SSRIs/SNRIs	0.50	(0.06, 0.96)	0.00%	8 (6-10)
Gabapentin	-0.13	(-0.46, 0.21)	0.08%	5 (3-8)
Isoflavones	-0.05	(-0.67, 0.57)	0.29%	6 (2-9)
Chinese herbal medicine	0.46	(-0.86, 1.9)	0.66%	8 (2-10)
Multibotanicals	-0.70	(-2.63, 1.51)	21.77%	3 (1-10)
Valerian root	-0.91	(-4.41, 1.69)	37.00%	2 (1-10)

Between-study heterogeneity: Standard deviation on the log MRs scale (SD) (95% CrI) 0.25 (0.01, 0.70)