

# Review: In menopause (intact uterus), estrogen + progestogen, isoflavones, and black cohosh reduce hot flashes

Sarri G, Pedder H, Dias S, Guo Y, Lumsden MA. **Vasomotor symptoms resulting from natural menopause: a systematic review and network meta-analysis of treatment effects from the National Institute of Health and Care Excellence guideline on menopause.** *BJOG*. 2017 Mar 9. [Epub ahead of print].

Clinical impact rating: ★★★★★☆

## Question

In women in natural menopause without hysterectomy, what are the relative efficacies of pharmacologic and nonpharmacologic treatments for vasomotor symptoms (VMSs)?

## Review scope

Included English-language studies compared hormonal and nonhormonal pharmaceuticals and nonpharmaceuticals with placebo for 4 to 26 weeks in women ≥ 45 years of age in natural menopause (amenorrhoea ≥ 12 consecutive mo) who had an intact uterus. Outcomes included frequency of VMSs and adverse events (treatment discontinuation and vaginal bleeding).

## Review methods

MEDLINE, EMBASE/Excerpta Medica, and Cochrane Library (all to Jan 2015) and reference lists were searched for randomized controlled trials (RCTs). 47 RCTs (*n* = 8326) assessing 16 treatment classes (placebo, sham acupuncture, nonoral estrogen plus progestogen, oral estrogen plus progestogen, conjugated estrogens plus bazedoxifene, tibolone, raloxifene, selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, gabapentin, isoflavones, Chinese herbal medicine, black cohosh, multibotanicals, valerian root, relaxation, and acupuncture) met selection criteria. Risk for bias was low (14 RCTs), moderate (19 RCTs), high (12 RCTs), or very high (2 RCTs). 32 RCTs (*n* = 4165, 12 treatment classes) reported VMSs, 21 RCTs (*n* = 4829, 10 treatment classes) reported treatment discontinuation, and 5 RCTs (*n* = 1367, 5 treatment classes) reported vaginal bleeding.

## Main results

The main results of direct meta-analyses are in the Table. Network meta-analysis, which includes indirect comparisons, showed that nonoral and oral estrogen plus progestogen did not differ from each other for VMSs, and neither differed from isoflavones or black cohosh. There were too few comparisons to evaluate vaginal bleeding.

## Conclusion

In women in natural menopause without hysterectomy, nonoral estrogen plus progestogen, isoflavones, and black cohosh reduce frequency of vasomotor symptoms more than placebo.

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## Commentary

Sarri and colleagues provide the most recent systematic review of the efficacy of hormone therapy and nonhormone options for hot flashes using conventional meta-analysis and network meta-analysis, which allows for comparison of treatments that have not been compared directly in RCTs. This evidence underpins the recent NICE guideline for management of menopause (1).

The results were generally consonant but partially at odds with previous meta-analyses (2-4): For women with a uterus, estrogen plus progestogen was most effective, particularly if applied transdermally, which reduces the potential effect of hormone therapy on coronary artery and cerebrovascular disease, venous thromboembolism, and cancer (5). Surprisingly, isoflavones and especially black cohosh (an extract from the root of the wild North American plant *Cimicifuga racemosa*) showed benefit. Other over-the-counter botanicals, selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, gabapentinoids, mind-body-based therapies, and acupuncture were no more effective than placebo. The review could not meaningfully assess the relative adverse effects beyond finding increased vaginal bleeding with hormone therapy.

The results suggest that women < 60 years of age who have severe and incapacitating hot flashes and no contraindications to hormone therapy (history of, or moderate-to-high risk for, breast cancer, coronary artery disease, stroke, or venous thromboembolism [6]) will probably obtain relief. The best choice for women with a uterus is low-dose estrogen, ideally given transdermally, with a progestogen. Estrogen alone is recommended for women without a uterus. For those who have less-intense vasomotor symptoms, contraindications, are > 60 years of age, or who prefer not to take hormone therapy, isoflavones or black cohosh may be worth trying. Also, many of the therapies that were not effective for vasomotor symptoms may be effective for such other limiting symptoms of menopause as mood swings, depression, and altered sleep (7).

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### Treatments for menopausal vasomotor symptoms vs placebo in menopausal women without hysterectomy\*

Outcomes	Treatment	Mean ratio (95% CrI) at 4 to 26 wk
VMS frequency	Nonoral estrogen + progestogen	0.23 (0.09 to 0.57)
	Oral estrogen + progestogen	0.52 (0.25 to 1.06)
	Isoflavones	0.62 (0.44 to 0.87)
	Black cohosh	0.40 (0.17 to 0.90)
	SSRIs/SNRIs	0.84 (0.54 to 1.31)
		<b>Odds ratio (CrI)</b>
Treatment discontinuation	Oral estrogen + progestogen	0.61 (0.37 to 0.99)
	Conjugated estrogen + bazedoxifene	0.31 (0.10 to 1.00)
	SSRIs/SNRIs	1.66 (1.07 to 2.61)

\*CrI = credible interval; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; VMS = vasomotor symptom; other abbreviations defined in Glossary. Table includes results of meta-analyses of direct comparisons.

## References

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