ISRCTN32277407 https://doi.org/10.1186/ISRCTN32277407

Oxybutynin or venlafaxine for hot flushes in women who cannot or prefer not to use hormone replacement therapy

Submission date
26/05/2023

Recruitment status
Not yet recruiting

Registration date
01/11/2023

Overall study status
Ongoing

Last Edited
27/09/2024

Condition category
Urological and Genital Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English Summary

Background and study aims
Most menopausal women experience vasomotor symptoms (VMS), including hot flushes and night sweats, lasting several years. They can have a significant impact on the lives of affected women. Hot flushes can be particularly severe for women taking endocrine therapies for treatment of breast cancer. Hormone replacement therapy (HRT) is the most effective treatment for hot flushes. However, some women are unable to take HRT because of other health conditions, such as a history of breast cancer. Others may choose not to take HRT because of concerns about the potential harms of HRT. All non-hormonal drugs are less effective than HRT and have side-effects.
The most commonly prescribed non hormonal treatment for menopausal hot flushes is called venlafaxine. There is evidence that oxybutynin, a medicine currently used to treat an overactive bladder, is effective in reducing the frequency of hot flushes and could be more effective than venlafaxine. We want to find out which of venlafaxine or oxybutynin is best for the relief of menopausal hot flushes.

Who can participate?
We will recruit 480 participants who are experiencing menopausal VMS symptoms but are unable to take HRT and 480 participants who prefer not to take HRT.

What does the study involve?
Participants will be randomly allocated to either oxybutynin or venlafaxine, and asked to take this treatment for 12 months. Participants will also be asked to keep a diary about their hot flushes and complete questionnaires at various points throughout the trial.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
Risk of inconvenience: Participants recruited in the hospital setting, may be required to stay in clinic a little longer than usual due to their participation in the trial when they first join. Trial

processes have been simplified as much as possible to ensure participants can complete most of the trial data electronically. Where hospital trusts do not post trial treatments, then participants will be expected to collect their treatment.
Risk of harm: NICE guidelines recommend venlafaxine for menopausal symptoms in women with breast cancer. Oxybutynin is not licenced for menopausal symptoms. However, both medications have marketing authorisation for use for other conditions and have been used in other clinical trials for menopausal symptoms, their side effects are known and well documented. Adverse event data will be collected regularly during the trial (week 4,8,12,6, and 12 months). Adverse events will be patient reported via a questionnaire. At the week 12 follow up appointment, the research team will ask about adverse events, if patients have not completed questionnaire data. If an SAE is reported, the NCTU will be made aware (within 24 hours of the participant disclosing an SAE via a questionnaire or to the research team). The NCTU and the recruiting site may be asked to contact the participant to obtain further information to determine whether an event has occurred that fulfils the SAE criteria. The seriousness and causality will be reviewed independently by a medical monitor (the Chief Investigator) responsible for determining causality assessments.
Consent training: this will be provided to site research teams, so that they can ensure randomised women are prepared to accept either allocation, understand the titration schedule and the need to balance benefit against side effects. The research clinicians at sites and their research support staff will be contactable for participants throughout the trial, should they experience any symptoms or side effects. Participants will be supplied with a trial treatment leaflet, which will explain the dose escalation schedule.
The inclusion/exclusion criteria ensures that only those who cannot or do not want to use HRT will be included in the trial. The trial will not be conveyed as an alternative equivalent to HRT.
Risk of breach of confidentiality: All members of the research team will have undergone GCP training. No personal information will be sent to the research team prior to receiving a 'consent to contact' form from the potential participant. The REDCap database is designed so only relevant members of the research team can see outcome measures of their participants. It is a validated secure web-based platform which allows for data tracking via date stamped audit logs. REDCap meets GCP standards.
Pregnancy: women experiencing the menopause/perimenopause may become pregnant. To note those in the 'prefer not to use HRT group' will need to be over 45 years of age to be eligible. PPI feedback suggests that requesting perimenopausal women to use highly effective contraception may be a barrier to recruitment. Also, many of the highly effective methods are hormonal, which they do not wish to use or cannot. PPI feedback also suggested that asking about contraception could be problematic for some women, especially those from faith groups, who may not want to use or consider contraception. PPI felt that women would prefer the research team to be up front about the medication and the associated risks. They can cope with transparency and want to make informed decisions.
According to the BUMPS website (https://www.medicinesinpregnancy.org/Medicine--pregnancy/Venlafaxine/) most studies of pregnant women taking venlafaxine do not raise concern that it causes birth defects, stillbirth, preterm delivery, or low infant birth weight. However, for some pregnancy outcomes, only small numbers of women have been studied and ongoing research is ideally required. Similarly, with Oxybutynin (https://www.medicinesinpregnancy.org/Medicine--pregnancy/Oxybutynin/) there is limited research on its use during pregnancy, but there was no indication of any increased risk of miscarriage or birth defects in the babies.
Given what is known about the risks of the trial treatments, PPI feedback and the numbers of women who may become pregnant during trial participation, we would put the following measures in place.
-Women who are pregnant, thinking of becoming pregnant in the next 12 months, or breastfeeding will be excluded from the trial. This is an eligibility exclusion criterion.
-The PIS will inform women about the risks of pregnancy while taking trial treatment and will

recommend the use of contraception, but it will not be compulsory. It will also explain that trial treatment would be stopped immediately if they become pregnant.
-Clinicians and site staff will be trained to discuss the risks associated with pregnancy prior to trial entry.

Where is the study run from?
University College London (UK)

When is the study starting and how long is it expected to run for?
May 2023 to August 2027

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
Dr Melanie Davies, melanie.davies@ucl.ac.uk

Contact information

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Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006998

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
139995, IRAS 1006998, CPMS 56795

Study information

Scientific Title
Oxybutynin or venlafaxine for hot flushes in women who cannot or prefer not to use hormone replacement therapy: randomised trial and economic evaluation

Acronym
BLUSH

Study hypothesis
Primary objective:
To compare the VMS, measured by weekly average Hot Flush (HF) score, at week 12, separately, in the two populations of women with menopausal VMS ((a) those that are unable to take HRT, and (b) those who prefer not to use HRT), after 3 months of treatment with extended-release oxybutynin or low-dose modified-release venlafaxine.

Secondary Objectives
1. Compare the relative effectiveness of extended-release oxybutynin compared to low-dose modified-release venlafaxine in controlling VMS at week 4, week 8, and at 6- and 12-months post-randomisation.
2. Compare treatment discontinuation at 12 months.
3. Evaluate the cost-effectiveness of oxybutynin, compared to venlafaxine.

4. Determine the tolerability (continuation of allocated drug) and participant-reported acceptability of oxybutynin and venlafaxine amongst women with VMS.
5. Assess the effectiveness of the trial drugs on quality of life, work and social productivity, mood, bladder function.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/09/2023, East Midlands - Leicester South Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8143; Leicestersouth.rec@hra.nhs.uk), ref: 23/EM/0138

Study design
Interventional double blind randomized parallel group controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Efficacy

Participant information sheet

Condition
Women experiencing menopausal and peri menopausal hot flushes

Interventions
To compare the relative clinical and cost-effectiveness of extended-release oxybutynin compared to low-dose modified-release venlafaxine in controlling VMS after 3 months of treatment, separately, in two populations of women with menopausal VMS: (a) those that are unable to take HRT, and (b) those who prefer not to use HRT. Participants will be recruited from secondary care clinics (which include gynaecology, specialist menopause, oncology), social media and GP/hospital database searches, throughout the UK.
During the recruitment process, eligibility will be checked, and consent will be obtained (either electronically or face to face). As part of the eligibility checks, participants will self-complete a hot flush diary, and report the number and severity of hot flushes every day, for 7 days, and only those with a mean of ≥ 5 moderate/severe hot flushes per day will be eligible to take part. Baseline data will be recorded, which will include demographics, body mass index, when hot flushes started, history of hysterectomy, reason for contraindication to HRT (Group A), lifestyle factors, use of medication, complementary and supplements. Participants will also be sent baseline questionnaires to self-complete about their quality of life, hot flushes, overall health and wellbeing, urinary symptoms, sleep, and work productivity.

Eligible participants who consent will be individually randomised on a 1:1 ratio, separately for the two participant groups, using an online randomisation system, minimised in a secure online algorithm by recruitment site, body mass index, and use of anti-oestrogens (group A) or recent hormone (HRT) use (group B), and retaining a random element. Investigators and participants will not be blinded.

Those allocated to oxybutynin will receive extended-release oral oxybutynin, prescribed at a starting dose of 5mg once daily, increasing by 5mg each week, if tolerated, to a maximum dose of 15 mg. Those allocated to venlafaxine will receive modified-release oral venlafaxine, prescribed at a starting dose of 37.5mg once daily, increasing by 37.5mg at week 2 if tolerated, to a maximum dose 75mg.

The doses for both treatments should be escalated if the participant perceives they are gaining benefit, or reported side effects precludes further dose increases. If necessary, the participant can reduce dose to the last tolerated dose. Participants will be advised to take trial treatment until month 12.

Participants will attend follow up appointments (face to face/ telephone/video) with their trial clinician/nurse who will conduct a clinical review at approximately 3, 6 and 9 months. Participants will also be asked to self-complete questionnaires at 4, 8, 12 weeks and 6- and 12-months post randomisation. The questionnaires will include questions about quality of life, hot flushes interference, overall health and wellbeing, adherence and problems with treatment, impressions of their treatment, urinary symptoms, sleep and work productivity. Participants will also be required to complete a daily hot flush diary, over a 7 day period at these time points too.

Participants may withdraw from the study at their own request at any time and will be made aware that this will not affect their future care. Participants will also be made aware (via the information sheet and consent form) that should they withdraw from the study the data collected to date will not be erased and may still be used in the final analysis.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacoeconomic, Therapy

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Venlafaxine hydrochloride, oxybutynin hydrochloride

Primary outcome measure
The average Hot Flush (HF) score (frequency x severity) over one week, at week 12

Secondary outcome measures
All measured at baseline, week 12, and 6 and 12 months and additional stated timepoints:
1. Average HF score (also in weeks 4 and 8)
2. Frequency and severity (individually) of hot flushes/night sweats (also in weeks 4 and 8)
3. Individual domains and total score of MENQOL-I (also at week 4)
4. Hot Flush Related Daily Interference Scale (HFRDIS) (also at week 4)

5. Health related quality of life (EQ-5D-5L) and capability-wellbeing (ICECAP-A)
6. Participant acceptability and satisfaction with treatment (also at week 4)
7. Participant-reported global impression of change on VMS and overall wellbeing
8. Urinary urgency, frequency and incontinence (ICIQ-OAB)
9. Sleep quality (PSQI)
10. Work Productivity and Activity Impairment Questionnaire- general (WPAI)
11. Pregnancy and pregnancy outcomes (participant reported and/or patient records)
12. Common known side-effects of each treatment (participant reported via questionnaires)
13. Change or cessation of treatment, and for breast cancer population, continuation of endocrine therapy (participant reported via questionnaires)
14. Resource Use (participant reported via questionnaires)

Overall study start date
24/05/2023

Overall study end date
31/08/2027

Eligibility

Participant inclusion criteria
Group A (HRT contraindicated)
1. Women for whom HRT is contraindicated, e.g. women with breast cancer treated with adjuvant endocrine therapy.
2. ≥5 moderate/ severe menopausal hot flushes daily average, collected over a week, prior to randomisation.
3. Written/electronic informed consent.

Group B (prefer not to use HRT)
1. Diagnosis of menopause or perimenopause
2. Age > 45 years
3. ≥5 moderate/ severe menopausal hot flushes daily average, collected over a week, prior to randomisation.
4. Not intending to use HRT within 12 months.
5. Written/electronic informed consent.

Participant type(s)
Other

Age group
Adult

Lower age limit
45 Years

Upper age limit
65 Years

Sex
Female

Target number of participants
960

Participant exclusion criteria
Group A (HRT contraindicated)
1. Age >65 years
2. Contraindications to either trial treatment
3. Pregnant or planning on becoming pregnant or breastfeeding
4. Breast Cancer patients with advanced stage cancer
5. Taking other pharmacological treatment for VMS*

Group B (prefer not to use HRT)
1. Age >65 years
2. Contraindications to either trial treatment
3. Pregnant or planning on becoming pregnant or breastfeeding
4. Transwomen
5. Women already on HRT or using hormonal treatment for gynaecological conditions or contraception*.

*Women already on HRT, or other treatments VMS, or who are using treatment for gynaecological conditions or contraception, who want non-hormonal treatment, are eligible if willing to stop their treatment for a ≥4-week washout period before entering the pre-randomisation eligibility screening phase. Women using a levonorgestrel-releasing intrauterine system (IUS), will not have to complete a washout or stop this treatment while in the trial, due to minimal systemic circulation of levonorgestrel.

Recruitment start date
30/04/2025

Recruitment end date
30/11/2025

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
-
United Kingdom
-

Sponsor information

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Sponsor type
University/education

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Peer reviewed scientific journals
Conference presentation
Publication on website
Submission to regulatory authorities
Anonymised participant data may be shared with researchers external to the trial research team in
accordance with the NCTU's data sharing procedure.

Intention to publish date

31/08/2028

Individual participant data (IPD) sharing plan

The datasets analysed during the current trial will be available upon request from the NCTU (ctu@nottingham.ac.uk), a minimum of 6 months after publication of the main results paper. Access to the data will be subject to review of a data sharing and use request by a committee including the CI and sponsor and will only be granted upon receipt of a data sharing and use agreement. Any data shared will be pseudo anonymised which may impact on the reproducibility of published analyses.

IPD sharing plan summary

Available on request