South Africa National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Gynaecology

MEDICINE REVIEW:

1. Executive Summary

Date: July 2018
Medicine (INN): SSRIs (fluoxetine, citalopram, sertraline, escitalopram, paroxetine)
Medicine (ATC): N06AB
Indication (ICD10 code): N95.1 Menopausal and female climacteric states
Patient population: Menopausal women with severe menopausal vasomotor symptoms (hot flushes).
Prevalence of condition: 80% of menopausal women, of which 20% will seek medical help.
Level of Care: Regional hospital level.
Prescriber Level: Obstetrician and gynaecologist
Current standard of Care: Hormone therapy
Efficacy estimates: (preferably NNT) n/a
Motivator/reviewer name(s): GS Gebhardt/E Bera
PTC affiliation: Tygerberg hospital

2. Name of author(s)/motivator(s)

Primary reviewer: GS Gebhardt
Secondary reviewer: E Bera

3. Author affiliation and conflict of interest details:

GS Gebhardt: Stellenbosch University, Adult Hospital Level Committee (2017-2020); no applicable conflict of interest declared.
E Bera: University of the Witwatersrand, Adult Hospital Level Committee (2017-2020); no applicable conflicts of interest.

4. Introduction/ Background

Menopausal hormone replacement therapy (HRT) including tibolone and conjugated equine estrogens are the most effective treatment for vasomotor symptoms (VMS) associated with menopause at any age (1). When there are contra-indications or poor response to HRT, selective serotonin reuptake inhibitors (SSRI, such as fluoxetine or citalopram) and serotonin-norepinephrine reuptake inhibitors (SNRI; such as venlafaxine and desvenlafaxine) have been shown to be effective in randomized controlled trials. The rationale of using antidepressant drugs is firstly, many patients with climacteric symptoms suffer from depressive symptoms and secondly, antidepressant drugs acting on synaptic serotonin concentrations may beneficially interfere with the pathophysiology of VMS (2).

5. Purpose/Objective (Research question in PICO format):

In women with post-menopausal symptoms who have contra-indications or a poor response to hormonal replacement therapy (HT) (P), does SSRI (I) relieve vasomotor symptoms (O) when compared to placebo or other non-hormonal treatment (C)?

6. Methods:

a. Data sources: Pubmed, Cochrane database of systematic reviews, ScienceDirect, NICE, Google scholar, EMBASE, SCOPUS, ISRCTN registry, EBSCOhost and SUNSearch.

b. Search strategy

("serotonin uptake inhibitors"[Pharmacological Action] OR "serotonin uptake inhibitors"[MeSH Terms] OR ("serotonin"[All Fields] AND "uptake"[All Fields] AND "inhibitors"[All Fields]) OR "serotonin uptake inhibitors"[All Fields] OR "ssri"[All Fields]) AND ("menopause"[MeSH Terms] OR "menopause"[All Fields]) AND (("Hot Flashes"[Mesh]) OR ("hot flashes" OR "hot flush" OR "vasomotor symptoms" OR "night sweats" OR "menopausal symptoms"))

c. Evidence synthesis

1. **<u>Systematic reviews</u>**
   a. **2010: Rada et al. Cochrane review- Non-hormonal interventions for hot flushes in women with a history of breast cancer (3).**
      - Included 16 RCT on non-hormonal therapies.
      - Included only six studies in the SSRIs and SNRIs section, with 451 women in total.
      - Could not pool data, so each study reported separately.
      - Cochrane conclusion: Clonidine, SSRIs and SNRIs, gabapentin and relaxation therapy showed a mild to moderate effect on reducing hot flushes in women with a history of breast cancer.
      - Only 2 studies on SSRIs included:
        1. Kimmick et al 2006 (4): Randomized, double-blind, placebo-controlled, crossover study of sertraline for the treatment of hot flashes in 62 women (only 39 completed the 12 weeks).
           a. Sertraline was significantly more effective than placebo in reducing hot flash frequency (p=0.03) and women preferred sertraline to placebo
        2. Stearns et al 2005 (5): stratified, randomized, double-blind, cross-over, placebo-controlled trial to investigate the efficacy of paroxetine 10 mg and 20 mg compared to placebo in 151 women.
           a. Paroxetine 10 mg reduced hot flash frequency and composite score by 40.6% and 45.6%, respectively, compared to 13.7% and 13.7% for placebo (P =0.0006 and P = .0008, respectively). Paroxetine 20 mg reduced hot flash frequency and composite score by 51.7% and 56.1%, respectively, compared with 26.6% and 28.8% for placebo (P = .002 and P = .004, respectively). **Efficacy was similar between the two doses**, but women were less likely to discontinue low-dose paroxetine.

   b. **2013: Shams et al. SSRIs for Hot Flashes: A Systematic Review and Meta-Analysis of Randomized Trials (6).**
      - Identified 61 randomized trials, 11 studies included, studies included 2,069 women in total.
      - List of included studies:
        - **Paroxitene (3 studies):**
          - <u>Simon et al 2012</u> (7) (same study also published in different journal in 2013 (8)
            - This was actually two studies- both RCT with blinding, the first lasting 12 weeks and then a second trial over 24 weeks to see if the effect persists.
            - 614 women in the 12 week study and 570 in the 24 week study receiving either paroxitene 7.5mg or placebo.
            - In both studies, paroxetine 7.5 mg reduced the frequency and severity of moderate to severe vasomotor symptoms compared with placebo.
            - The observed reduction remained statistically significant throughout the studies; in the 24-week study, the proportion of responders was significantly greater in the paroxetine 7.5 mg arm than in the placebo

arm, thereby demonstrating persistence of treatment benefit with paroxetine 7.5 mg up to 24 weeks.

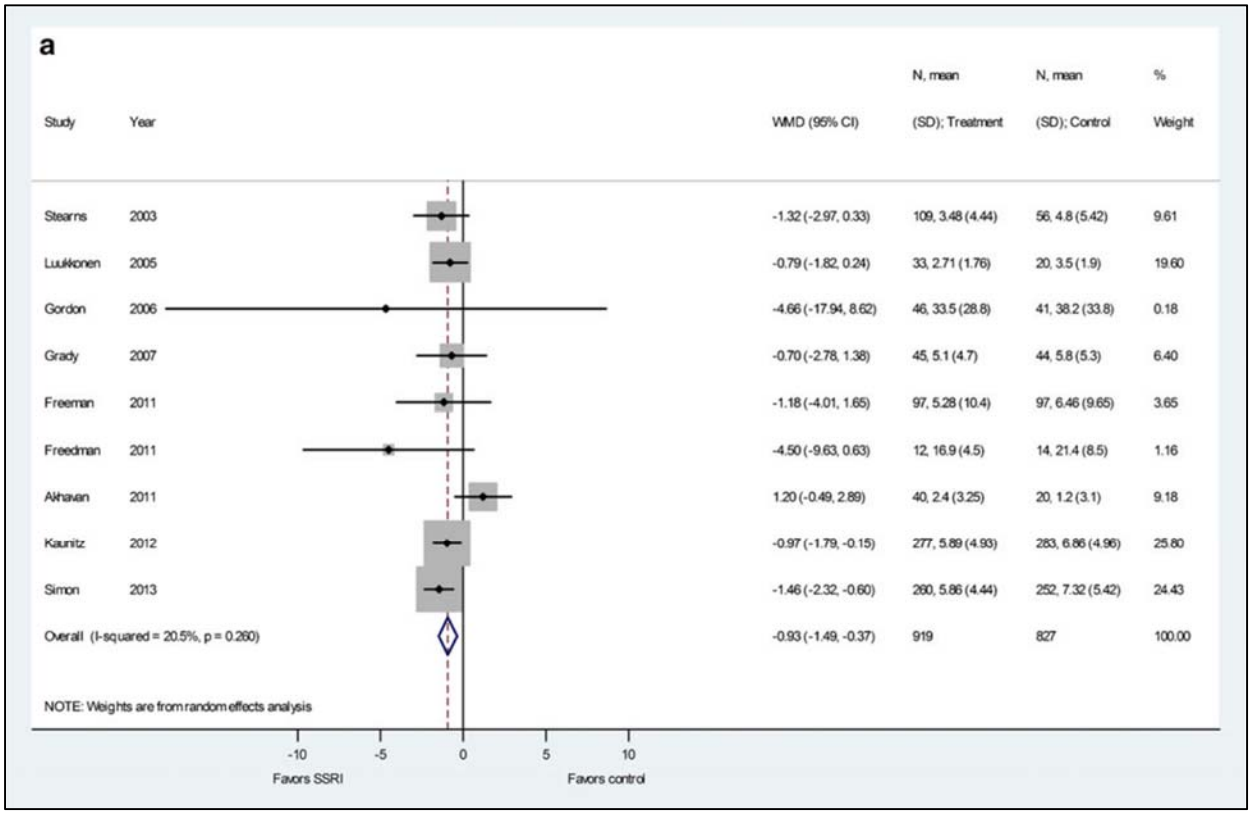
- The second article is referenced as *Kaunitz A, Sanacora G, Bhaskar S, Lippman J. Safety and efficacy of low-dose mesylate salt of paroxetine (LDMP) for the treatment of vasomotor symptoms (VMS) associated with menopause: A 12-week, randomized, placebo-controlled phase 3 study. Menopause. 2012;19(12):1389.* This is incorrect and the author (Kaunitz A) appears in two other articles in the 2012 edition of 'Menopause" but neither of them is this index article. It was therefore not possible to read this manuscript for the purpose of this review.
- Stearns et al 2003 (9): Paroxetine Controlled Release in the Treatment of Menopausal Hot Flushes
  - This was a randomized, double-blind, placebo-controlled parallel group study conducted across 17 sites
  - N=56 received placebo, n=51 received paroxitene 12.5mg/day and n=58 received paroxitene 25mg/day.
  - Mean placebo-adjusted reduction in hot flash scores were -4.7 (95% CI -8.1—1.3, p=0.007) in the low dose group and -3.6 (also (95%CI -6.8 to -0.4, p=0.03) in the 25mg group which equated to a median reduction of more than 60% in both groups as compared to placebo (reduction of 37.8%).

- **Escitalopram**
  - Freeman 2011 (10) Efficacy of escitalopram for Hot Flashes in Healthy Menopausal Women: A Randomized Controlled Trial.
    - Randomized, double-blind, placebo-controlled, parallel arm trial for 8 weeks in a sample stratified by race
    - Randomised to 10mg escitaolpram per day, increased to 20mg in a blinded manner at week 4 for non-improving participants
    - N=205 in total
    - Reduction in hot flash frequency was greater in the escitalopram group versus placebo (−4.60, SD 4.28 and −3.20, SD 4.76, respectively, P=0.004)
- **Citalopram**
  - Akhaven et al 2011 (11) Comparison of the therapeutic effects of fluoxetine, citalopram, estrogen and progesterone and placebo in the treatment of hot flushes in perimenopausal women
    - This was published in Kurdish and there is only an English abstract
    - According to the abstract, the biggest reduction in hot flushes was in the placebo group.
  - Kalay 2001 (12): Efficacy of citalopram on climacteric symptoms
    - 100 postmenopausal women who were allocated into one of four groups: (1) citalopram, (2) placebo, (3) citalopram + HT, or (4) placebo + HT.
    - After week one the dose of citalopram was increased form 10mg/day to 20mg/day
    - Mean hot flash scores significantly improved in all groups ($P < 0.05$) but it was significantly greater in the citalopram groups ($p<0.01$).
  - Suvanto-Luukkonen et al 2005 (13) Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study
    - Placebo-controlled double-blind study with a follow-up period of 9 months, n=150
    - Randomised in three groups- placebo, citalopram and fluoxetine

        - Compared with placebo, citalopram (10mg increased to 20mg then 30mg) and fluoxetine (10mg increased to 20mg then 30mg) had little effect on hot flushes and therefore this small study did not recommend it for the treatment of menopausal symptoms.
- **Sertraline**
    - Aedo et al 2012 (14) Sertraline improves the somatic and psychological symptoms of the climacteric syndrome (brief report)
        - 44 women, RCT, 39 completed the trial, allocated to either placebo or sertraline 50mg.
        - They reported an odds ratio of 7.94 (95% confidence interval 1.3–57.3), p = 0.0038 for the sertraline group, presumably odds for *not* having hot flushes
        - Also large reduction in the placebo group.
    - Grady et al 2007 (15) Ineffectiveness of Sertraline for Treatment of Menopausal Hot Flushes: A Randomized Controlled Trial
        - This was a randomized, blinded, placebo-controlled trial in women aged 40 to 60 years with 14 or more hot flushes per week (N=99)
        - Treatment with sertraline did not improve hot flush frequency or severity, but was associated with bothersome side effects.
    - Gordon et al 2006 (16) Sertraline to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general population
        - N=102
        - RCT, starting with sertraline 50mg or placebo before cross-over
        - Women only experienced five fewer hot flashes per week than they did on the placebo, although this was significant (P = 0.002). The severity of hot flashes was not significantly different.

The overall pooled results showed:

- The use of SSRIs was associated with a statistically significant decrease in the number of hot flashes per day after 8 weeks of use (Mean Difference −0.93; 95 % CI −1.49 to −0.37), see below.
- The effect of SSRIs on the frequency of hot flashes compared to estrogen, the most effective alternative treatment, was smaller.



Overall impression and assessment of quality of evidence for the Sham review:

- The review specifically excluded patients with cancer, so the results cannot be extrapolated to these patients (who also experience hot flushes related to tamoxifen)
- The authors stated that they followed all the principles of conducting systematic reviews of the Cochrane collaboration and the PRISMA statement, but details not specified.
- There is an extensive section on risk of bias, using the Cochrane risk of bias tool.
- Appraised using the AMSTAR-2 tool; found to be of sufficient quality to make a recommendation.

c. 2015 Handley et al. The efficacy and tolerability of SSRI/SNRIs in the treatment of vasomotor symptoms in menopausal women: A systematic review (17).

- 18 RCTs; no meta-analysis done
- All studies evaluated hot flashes through a validated, self-reported, daily hot flash diary, recording frequency and severity.
- None of the included studies were published after the review period of Shams, and the extra ones included in this review had non-significant findings or inadequate power sizes so would not benefit from meta-analysis.
- Assessed using AMSTAR-2. Although the title is a 'systematic review' the article is in fact only a literature review. There was a very limited search for literature done (only three databases) with no explanation of why studies were excluded. No assessment for risk of bias was done and only English language literature was searched.
- This review does not add any additional information that is not already discussed in the Sham review.

d. Grant et al 2015. Menopausal Symptoms: Comparative Effectiveness of Therapies (18)

- This is a comprehensive (490 pages and 375 included articles) overview that includes several systematic reviews, network reviews and meta-analyses.

- The design was rigorous and there is extensive discussion of the selection criteria, search strategies, risk of bias and methodology
- The review was assessed for quality using the AMSTAR-2 tool and found to comply with most of the criteria.
- It includes all available strategies to address menopausal symptoms.
- The section on SSRI/SNRIs and vasomotor symptoms included 13 studies (some studies that were not in the Shams meta-analysis were included).
- There were 13 comparisons of SSRIs or SNRIs (including escitalopram, venlafaxine, desvenlafaxine, citalopram, fluoxetine, and paroxetine) with placebo and they were rated as four good, three fair, and six poor quality trials.
- The standardized mean difference was precise and effect differed from placebo (-0.37; 95% CrI: -0.51 to -0.23), it was similar limited to the good and fair quality trials in a pairwise analysis (-0.33; 95% CI: -0.42 to -0.24; tau2=0.006), or those of venlafaxine or desvenlafaxine alone (-0.36; 95% CI: -0.55 to -0.17; tau2=0.04; 6 trials).
- The strength of evidence that SSRIs or SNRIs improve hot flush symptoms compared with placebo is rated high (see forest plot below).

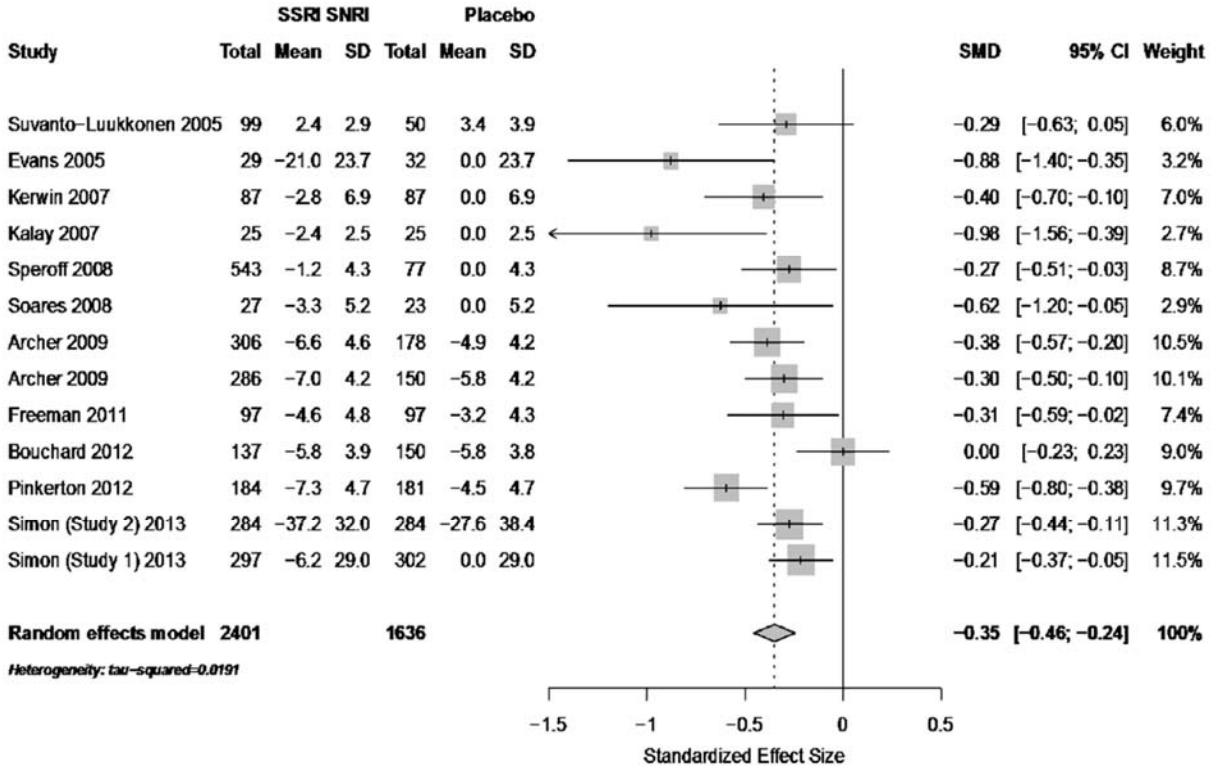


Table below shows the magnitude and strength of evidence of all available treatments for vasomotor symptoms, with SSRIs just below HRT and better than gabapentin, black cohosh and ginseng.

Table A. Magnitude and strength of evidence of treatments for vasomotor symptoms: standardized mean differences from pairwise comparisons

Number of Comparisons	Comparators	Effect Size (SMD) (95% CI)	Strength of Evidence
9	Estrogen (high) vs. placebo	-0.50 (-0.61 to -0.39)	High
39	Estrogen (standard) vs. placebo	-0.64 (-0.74 to -0.53)	High
53	Estrogen (low/ultralow) vs. placebo	-0.55 (-0.61 to -0.48)	High
13	SSRI/SNRI vs. placebo	-0.35 (-0.46 to -0.24)	High
5	Gabapentin vs. placebo	-0.28 (-0.38 to -0.19)	Moderate
35	Isoflavones vs. placebo	-0.31 (-0.41 to -0.22)	Low
4	Black cohosh vs. placebo	-0.31 (-0.46 to -0.15)	Low
3	Ginseng vs. placebo	-0.17 (-0.43 to 0.09)	Low

CI = confidence interval; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

e. Johns et al 2016: Informing hot flash treatment decisions for breast cancer survivors: a systematic review of randomized trials comparing active interventions (19)

- 13 RCTs reviewed.
- Because of heterogeneity in both intervention and outcome measures, unable to pool estimates for a meta-analysis or derive strengths of recommendations based on the GRADE approach.
- Dose-related evidence:
  1. Citalopram 10, 20, and 30 mg daily had comparable outcomes
  2. Paroxetine 10 mg daily had fewer side effects than 20 mg
  3. Venlafaxine 75 mg daily improved hot flashes without additional side effects from higher dosing.
- The systematic review part was done according to a rigorous design described in full in the text. It was assessed by the AMSTAR-2 tool and the parts related to the systematic review was found to be of high quality.

2. <u>Randomized trials of SSRIs specifically published since 2015 and not included in the above meta-analyses</u>

i. Freeman et al 2016. Efficacy of **escitalopram** for Hot Flashes in Healthy Menopausal Women: A Randomized Controlled Trial (11)
   a. Randomized, double-blind, placebo-controlled, parallel arm trial for 8 weeks (n=205).
   b. At week 8, reduction in hot flash frequency was greater in the escitalopram group versus placebo (−4.60, SD 4.28 and −3.20, SD 4.76, respectively, P=0.004).

ii. 2016 Capriglione et al. Role of **paroxetine** in the management of hot flashes in gynecological cancer survivors: Results of the first randomized single-center controlled trial (20).
   a. Randomized, double-blind, placebo-controlled study, postmenopausal women with a prior history of gynecological cancer who had completed active cancer treatment; n=81; 7.5 mg oral paroxetine vs placebo daily for 16 weeks.
   b. Sleep and hot flashes were assessed at baseline, week 4 and week 16.
   c. The mean weekly reductions in VMS frequency were significantly greater for paroxetine 7.5 mg than for placebo on week 4 (−31.0 and −21.5, respectively; p=0.0001) and week 16 (−46.5 and −39.3, respectively; p = 0.0090)

iii. 2015 Davari-Tahna et al. Comparison of **citalopram** and venlafaxine's role in treating sleep disturbances in menopausal women, a randomized, double-blind, placebo-controlled trial (21)
   a. randomized, double-blind, placebo-controlled clinical trial was conducted in three groups of 20 postmenopausal women - venlafaxine 75 mg/daily vs citalopram 20 mg/d vs placebo.

b. The frequency of hot flashes in a day was reduced significantly by both citalopram and venlafaxine ($p<0.05$), although it was more reduced by citalopram than venlafaxine ($p = 0.03$).
c. No effect size given.

iv. 2015 Rahmanian et al. A crossover study comparing gabapentin and **fluoxetine** for the treatment of vasomotor symptoms among postmenopausal women (22).
   a. randomized crossover study (39 women in each group)
   b. Both drugs significantly reduced the severity of night sweats for both groups: compared with baseline measures, fluoxetine reduced the severity of night sweats in group A by 18% ($P = 0.001$) and in group B by 41% ($P = 0.001$); and gabapentin reduced the severity of night sweat in group A by 56% ($P = 0.001$) and in group B by 62% ($P = 0.001$).
   c. Gabapentin caused greater reductions in the severity of hot flashes than did fluoxetine ($P<0.001$)
   d. No effect size given

7. Evidence quality

The published studies suffer from major methodological weaknesses. At least 2 of the 13 included studies had some industry support – either direct supply of study drugs, or honoraria for the authors. In a number of studies, no competing interests were declared by the authors.

In many of the included RCTs only double digit participants (<100) were enrolled, follow up was brief (<12 weeks of treatment). Almost all of the included studies measured reduction in vasomotor symptoms as an endpoint, rather than the resolution of VMS. Very few studies reported ">50% reduction in VMS" as a dichotomous endpoint. Almost all studies compared SSRIs/SNRIs with placebo. There were very few head-to-head studies which compared one SSRI against another. Some studies were cross-over trials, making it even more difficult to draw definitive conclusions about the validity of their results.

The placebo effect was high (up to 40%) in some studies; almost all studies showed superiority of SSRIs/SNRIs over placebo, although the effect size is questionable.

Some studies reported on quality of life indicators, including sleep/depression, but not a single study evaluated long-term outcomes, e.g. stroke, ischaemic heart disease, VTE, cancer, fragility fractures or osteoporosis.

8. Alternative agents:

Clonidine, oral could possibly be considered for review (though not included in this review).

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	MA
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. SSRIs: fluoxetine, citalopram, escitalopram, paroxetine.	Rationale for therapeutic alternatives included: References:
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	Cost of medicines/ 30 days: **Medicine** / **Cost (ZAR)** Fluoxetine 20mg daily: 5.46* Citalopram 20mg daily: 7.52* Paroxetine 20mg daily: 4.95 to 9.99** Escitalopram 10mg daily: 28.09 to 56.19** *Contract circular HP09-2016SD ** SEP database, 28August2018: Range of 30 to 60% of SEP **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☒	☐	☐

Recommendation: Based on this evidence review, the Adult Hospital Level Committee reccomends SSRIs for menopausal symptoms, where there is poor response to HT or where HT is contra-indicated. However, citalopram is preferred over fluoxetine in women taking concomitant tamoxifen.

Rationale: Evidence of effficacy for SSRI and the need for an alternative for HT, in women where HT is contra-indicated, is poorly tolerated or not effective. SSRIs/SNRIs has generally been shown to be more effective than placebo at reducing vasomotor symptoms and menopause in the short-term, but their long-term benefits (or harms) are largely unknown. Citalopram is preferred over fluoxetine, as there is more data for citalopram, though of low methodological quality and the drug-drug interaction of fluoxetine with tamoxifen should be considered.

Level of Evidence: III RCT with disease-oriented outcomes

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 27 SEPTEMBER 2018:

NEMLC accepted the medicine review, and recommended that where hormone therapy for menopausal symptoms, is contra-indicated, poorly tolerated or ineffective that:

- Fluoxetine, oral is recommended as first line therapy in this cohort of patients.
- Citalopram, oral, be recommended with concomitant tamoxifen.

Monitoring and evaluation considerations

Research priorities

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