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OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary
Hormone therapy for menopausal women with low libido

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BACKGROUND

Menopause is the permanent end of menstruation and fertility but, even before the true onset of menopause, women may experience menopausal symptoms and changes in their menstrual cycle (NAMS 2012). The most common symptoms associated with menopause are hot flushes, night sweats, sleep disturbance, vaginal atrophy, and dyspareunia (NAMS 2012). In order to alleviate these symptoms, some women start using menopausal hormone therapy (HT) (NAMS 2012; Santen 2010).

According to the Diagnostic and Statistical Manual of Mental Disorders, DSM V (American Psychiatric Association 2013), sexual dysfunction is defined by disturbances in sexual desire and by psychophysiological changes that characterize the sexual response cycle, causing marked distress and interpersonal difficulty. Sexual functioning is of great importance for quality of life, as approximately 75% of middle-aged American women consider sexual activity as being of moderate to extreme importance (Cain 2003). Despite its importance, female sexual function is not easy to define or investigate because it depends on several factors such as health and well-being, cultural habits, socioeconomic status, relationship issues, and existence and health of the partner (Davis 2009). Female sexual dysfunction might be evaluated in different domains, including sexual interest and arousal, orgasm and pain (Binik 2010). Although sexual function declines throughout the menopause transition (NAMS 2012; Rosen 2011), it is unclear whether this is caused by the low estrogen levels, aging, or both (da Silva Lara 2009; Nappi 2009). The objective of this evidence brief is to assess the benefits of hormone therapy for menopausal women with low libido.

ASK THE QUESTION

Question 1: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)?

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SEARCH FOR EVIDENCE

Databases included Ovid MEDLINE, MEDLINEinprocess, the Cochrane Central Register of Controlled Trials (CCRCT) & Cochrane Database of Systematic Reviews (CDSR).

1. exp Libido/ (4758)
2. exp Sexual Dysfunctions, Psychological/ (24675)
3. exp Sexual Dysfunction, Physiological/ (27985)
4. 1 or 2 or 3 (34837)
5. (libido* or ((sex* or coit* or intercours* or copulat*) adj3 (driv* or desir* or arous* or want* or need* or function* or dysfunction* or initia* or participa*))).mp. (45106)
6. ((reduc* or low* or decreas* or hypoactiv* or rais* or increas* or high* or elevat*) adj3 (driv* or desir* or arous* or function* or dysfunction* or want* or need* or function* or initia* or participa*)).mp. (364319)
7. exp sexual behavior/ (98928)
8. 5 or 6 (404317)
9. 7 and 8 (15626)
10. exp Estrogen Replacement Therapy/ (15127)
11. exp Estrogens/ad, tu [Administration & Dosage, Therapeutic Use] (28325)
12. 10 or 11 (39129)
13. exp Phytotherapy/ (37382)
14. exp Plants, Medicinal/ (58063)
15. exp Plant Preparations/ (195394)
16. exp Complementary Therapies/ (211582)
17. (acupunct* or acupress* or electroacupunct* or moxibust* or holistic* or homeopath* or ayurved* or (mind adj body) or mindful* or meditat* or (relax* adj (therap* or treat*)) or tai chi or tai ji or naturopath* or phytother* or (medic* adj (herb or plant*)) or aromather* or yoga).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (122853)
18. 13 or 14 or 15 or 16 or 17 (430689)
19. 12 or 18 (468579)
20. 4 and 19 (1406)
21. 9 and 19 (465)
22. 20 or 21 (1642)
23. limit 22 to humans (1540)

24. limit 23 to female (994)
25. limit 24 to (meta analysis or systematic reviews) (68)
26. limit 24 to (controlled clinical trial or guideline or randomized controlled trial) (161)
27. limit 24 to (comparative study or evaluation studies) (82)
28. exp Epidemiologic Studies/ (2177321)
29. 24 and 28 (135)
30. 25 or 26 or 27 or 29 (355)
31. 24 not 30 (639)

Filters/limits included articles published in English in the last 10 years.

CRITICALLY ANALYZE THE EVIDENCE

The literature search resulted in numerous studies reporting on the benefits of hormone therapy for menopausal women with low libido. In order to simplify the process, the evidence appraisal tables have been grouped between the following modalities reporting on the outcomes of benefits: (1) Combined Hormone Therapy; (2) Estrogen; (3) Conjugated Estrogen; (4) Conjugated Estrogen/Bazedoxifene; (5) Fesoterodine and Estrogen; (6) Estrogen-progestogen therapy; (7) Estradiol; (8) Tibolone; (9) Tibolone vs. Hormone Therapy; and (10) Estrogen with Testosterone.

1. **Combined Hormone Replacement Therapy:** Two studies were found evaluating the effects of different hormone replacement therapies (HRT) on sexual function. One RCT (Genazzani 2011), randomized women into three groups receiving either, dehydroepiandrosterone (DHEA 10 mg) daily, or daily oral estradiol (1 mg) plus dihydrogesterone (5 mg), or daily oral tibolone (2.5 mg) for 12 months. The groups receiving DHEA or HRT reported a significant improvement in sexual function compared to baseline ($p < 0.001$ and $p < 0.01$, respectively) using the McCoy total score. The quality of relationship was similar at baseline and after 3, 6 and 12 months of treatment. There were significant increases in the numbers of episodes of sexual intercourse in the previous 4 weeks in women treated with DHEA, HRT and tibolone in comparison with the baseline value ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). One cross-sectional study (Tucker 2016), collected data via a questionnaire and serum test for testosterone and free androgen index (FAI). The questionnaire comprised demographic data and validated measures of sexual function, sexual distress, relationship satisfaction, body image, psychological stress, menopause quality of life and general quality of life. HRT use reduced the rates of dyspareunia ($p=0.027$) and the severity of sexual menopausal symptoms ($p=0.030$). Androgen levels were not significantly associated with desire or arousal scores.
   Quality of Evidence: Low

2. **Estrogen:** Three studies were found investigating the benefits of estrogen for menopausal women with low libido. One systematic review (Nastri 2013) included three studies and found that for estorgens alone versus control, in symptomatic or early postmenopausal women the SMD and 95% CI were compatible with a small to moderate benefit in sexual function for the HT group (SMD 0.38, 95% CI 0.23 to 0.54, P < 0.00001, high-quality evidence). One RCT (Fernandes 2014) randomized women to treatment with topical vaginal estrogen, testosterone, polyacrylic acid, or oil lubricant alone, three times a week for a period of 12 weeks. After treatment, estrogen produced improvements in the FSFI domains of sexual desire, lubrication, satisfaction, reduced pain during intercourse, and total score compared with lubricant alone. (P < 0.001). A comparative study (Setty 2016) divided women into three groups: group 1 remained on hormone therapy (HT)/estrogen therapy (ET); group 2 resumed HT/ET after stopping for at least 6 months, and group 3 stopped HT/ET and have not resumed. There was no statistically significant difference in sexual quality of life, dyspareunia, vaginal dryness, urinary tract infection, or married or married-like relationship across the three groups. However, for group 3 and sexual quality of life in particular, those who used VE had higher scores on the sexual quality-of-life scale than those who did not use VE (P=0.007). Comparative study results were inconsistent from systematic review and RCT.
   Quality of Evidence: Low

3. **Conjugated Estrogen:** Two RCTs were found evaluating the effect of conjugated estrogens in postmenopausal women. The first RCT (Freedman 2009), randomized women with symptoms of vulvovaginal atrophy (VVA) to either 1 g SCE-A cream or matching placebo for a period of up to 12 weeks. Efficacy was assessed at 2, 3, 4, 8, and 12 weeks and included the change from baseline in the severity of the most bothersome symptom (MBS), maturation index, and pH. Most women identified vaginal dryness as the MBS (48%) followed by pain with intercourse (31.3%). A statistically significant increase in the maturation index (P < 0.0001) and significant decreases in pH (P < 0.0001) and severity of the MBS (P < 0.0001) were observed for those treated with SCE-A vaginal cream compared with placebo. In the second RCT, (Gast 2009) women were randomized to one of two treatment groups: group A received estrogen plus progestogen therapy (EPT) with daily oral low-dose CE (PREMARIN)/medroxyprogesterone acetate (MPA) (0.45 mg CE/1.5 mg MPA) for six 28-day cycles along with initial vaginal priming with 1 g CE(PREMARIN) cream (0.625 mg CE/g) intravaginally for the first 6 weeks. Group B received an oral placebo tablet daily for six 28-day cycles along with 1 g placebo cream, intravaginally, for the first 6 weeks. The estrogen plus progestogen (EPT) group had a significant decrease in the frequency of dyspareunia compared with baseline and placebo in an analysis of responses to the McCoy Female Sexuality Questionnaire. Also, EPT was associated with a significant improvement in a woman's level of sexual interest, frequency of orgasm, and pleasure of orgasm. There was no effect of EPT use on coital frequency. The EPT group had significant improvement in receptivity/initiation and relationship satisfaction ($P < 0.05$), although not in other BISF-W domains, versus placebo (BISF-W analysis) and significant improvement versus placebo on most Women's Health Questionnaire responses ($P < 0.05$).
   Quality of Evidence: Low

4. **Conjugated Estrogen/Bazedoxifene:** Three studies were found evaluating conjugated estrogens with bazedoxifene. One systematic review (Nastri 2013) found that when comparing bazedoxifene versus control for symptomatic or early postmenopausal women the observed effect was compatible with no effect to a moderate benefit for sexual function in the HT group (SMD 0.23, 95% CI -0.04 to 0.50, P = 0.09). In unselected postmenopausal women, the 95% CI was compatible with small harm to a small benefit (SMD 0.04, 95% CI -0.20 to 0.29, P = 0.72). One RCT (Abraham 2014) described the effects of conjugated estrogens/bazedoxifene (CE/BZA) using the menopause-specific quality of life (MSQOL). Significant improvements were found with both CE/BZA doses in vasomotor domain (-0.61 to -2.23 over 3-24 months) and total scores (-0.24 to -0.94) compared to the control. Significant improvement compared with placebo in sexual domain (-0.11 to -0.72) was observed with the higher dosage, and with the lower dosage in the vulvar-vaginal atrophy (-0.71 at month 3). Another RCT (Bachmann 2010) found two BZA/CE doses (BZA 20 mg / CE 0.45 or 0.625 mg) were associated with significant improvement in ease of lubrication score from baseline compared with placebo ($p < 0.05$) on the Arizona Sexual Experiences (ASEX) Scale, although there was no difference in the change in total score. The Menopause-Specific Quality of Life (MENQOL) questionnaire results at week 12 showed significant improvements in vasomotor function, sexual function and total scores with both BZA/CE doses vs. placebo or BZA 20 mg ($p < 0.001$).
   Quality of Evidence: Low

5. **Fesoterodine and Estrogen:** One RCT (Chughtai 2016) investigated the combination effect of anti-muscarinic medication (fesoterodine) and topical vaginal estrogen in the treatment of overactive bladder (OAB) and female dysfunction in postmenopausal women. Subjects were randomized into two groups, one receiving fesoterodine once daily with topical vaginal estrogen or fesoterodine once daily alone. If 4 mg fesoterdine was tolerated at 1-week, the dose was increased to 8 mg. After 12-weeks, the combination group had a significant improvement in OAB symptom severity ($p = 0.006$), OAB health-related quality of life (HRQL) ($p = 0.029$), and SQOL-F (0.0003). The fesoterodine alone group also had significant improvement in OAB symptom severity ($p < 0.0001$), HRQL ($p = 0.0002$), and Sexual Quality of Life-Female, SQOL-F (SQOL-F) ($p = 0.02$). When compared directly to the fesoterodine alone group, the combination group after 12-weeks had a reduced OAB symptom severity (10 versus 23.3; $p = 0.35$), higher HRQL (96.9 versus 84.6; $p = 0.75$), and higher SQOL-F (99 versus 81; $p = 0.098$). The total number of micturition over 3 d was significantly reduced in the combination group (45-26, $p = 0.03$) between baseline and 12-weeks.
   Quality of Evidence: Low

6. **Estrogen-progestogen therapy:** One systematic review and one RCT were found assessing the effect of estrogen-progestogen. The systematic review (Nastri 2013) found one study that combined estrogen and progestogen. For estrogens combined with progestogens versus control, in symptomatic or early postmenopausal women the 95% CI was compatible with a small to moderate benefit for sexual function in the HT group (SMD 0.42, 95% CI 0.19 to 0.64, P = 0.0003, moderate-quality evidence). The second study (Fonseca 2007) was carried out over a total of 12 consecutive months. Patients received 17beta-estradiol 2mg in combination with norethisterone acetate 1mg (Cliane) daily for 6 months in Group A or one placebo tablet daily for 6 months in Group B. After 6 months, the groups were crossed over and the patients were followed up for another 6 months. In group A there were fewer hot flashes ($F=22.85$, $p<0.01$) and an improvement in sexual interest ($F=5.55$, $p<0.05$). The sequence in which the medication was received resulted in a statistically significant difference with respect to dyspareunia ($F=9.65$, $p<0.01$) and satisfaction with the duration of penetration ($F=6.58$, $p<0.05$). In the intrapatient analysis of variation with respect to orgasmic capability and the presence of dialogue with partner regarding the couple's sexual life, whether the placebo was taken prior to or following hormone therapy was significant ($F=17.12$, $p<0.001$ and $F=7.10$, $p<0.05$, respectively).
   Quality of Evidence: Moderate

7. **Estradiol:** Two RCTs examined the effect of estradiol on sexual function in postmenopausal women. One study (Huang 2008), examined the use of ultralow-dose transdermal estradiol compared to placebo. Women randomly assigned to estradiol had a 4.3 point greater improvement in the vaginal pain/dryness domain relative to placebo (95% CI = 0.3-8.4, P = .04). No significant differences in frequency of sexual activity or other sexual function domains (desire, satisfaction, problems, or orgasm) were observed between treatment groups (P ≥ .10 for all). The second RCT (Kingsberg 2016) included in the appraisal, evaluated the effect of TX-004HR, an estradiol vaginal drug, on female sexual dysfunction in postmenopausal women with vulvar and vaginal atrophy (VVA). The study compared the effects of 12-week treatment with TX-004HR dosing of 4, 10, or 25 µg compared to placebo. All three TX-004HR doses increased the baseline total FSFI score after 12 weeks, with 10 µg (P < .05) and 25 µg (P = .0019) having a significantly greater effect than placebo. A similar trend was observed for the individual FSFI domains, with 10 and 25 µg significantly improving baselines scores for pain and lubrication at 12 weeks (P ≤ .015 for all vs placebo). Changes from baseline to week 12 in arousal (P = .0085) and satisfaction (P = .0073) were significantly greater for TX-004HR 25 µg vs placebo. All three TX-004HR doses were comparable to placebo in their effect on desire and orgasm.
   Quality of Evidence: Low

8. **Tibolone:** Five studies were founding assessing the benefits of tibolone for menopausal women with low libido. One systematic review (Nastri 2013) found that for tibolone versus control, in symptomatic or early postmenopausal women the 95% CI was compatible with no effect to a small benefit for sexual function in the HT group (SMD 0.13, 95% CI 0.00 to 0.26, P = 0.05, low-quality evidence). In unselected postmenopausal women, the 95% CI was compatible with no effect to a moderate benefit (SMD

0.38, 95% CI 0.04 to 0.71, P = 0.03, low-quality evidence). Another systematic review (Formoso 2016), found that Tibolone was more effective than placebo (standard mean difference (SMD) -0.99, 95% confidence interval (CI) -1.10 to -0.89) for vasomotor symptoms. but removing trials at high risk of attrition bias attenuated this effect (SMD -0.61, 95% CI -0.73 to -0.49; odds ratio (OR) 0.33, 85% CI 0.27 to 0.41). Additionally, the systematic review found that Tibolone was associated with a lower rate of bleeding (OR 0.32, 95% CI 0.24 to 0.41; 16 RCTs; 6438 women). One RCT (Nijland 2007) randomized women to treatment with oral tibolone 1.25 mg or raloxifene 60 mg once daily for 2 years. In the raloxifene group, the WHQ vasomotor symptom domain showed consistently higher scores than in the tibolone group reflecting a worsening of vasomotor symptoms in the raloxifene group. Other domains showing statistically significant differences in favor of the tibolone group included depressed mood. There was little to no difference between the tibolone and raloxifene group in mean and median scores for the 4 domains (sexual interest, sex with partner, orgasm and vaginal lubrication) and the global score of the McCoy female sexuality questionnaire, short form at any of the post-baseline visits. Another RCT (Nijland 2008) randomized women to E2 (50 mg)/NETA (140 mg) in the form of a twice weekly patch plus a daily placebo tablet or tibolone 2.5 mg as a daily tablet with a twice weekly placebo patch. The FSFI score was greater with tibolone compared with E2. NETA approached statistical significance in the ITT analysis (P = 0.065). There was a statistically significant reduction in sexuality-related personal distress in both treatment groups when compared to baseline (P < 0.001 for both groups). No differences were observed between the groups. Satisfying sexual events increased from three to four times per 28 days at week 24 (P < 0.001 from baseline for both groups), with no difference between groups. Lastly, one prospective study (Kamenov 2007) conducted included two groups of clinically healthy postmenopausal women: a control group and a tibolone group. The Kupperman menopausal index (KI) was calculated for both groups at baseline and at six months. Sexual function was assessed by the Female Sexual Function Index (FSFI) questionnaire at the beginning and at the end of the study. The results showed that during the observation period KI decreased significantly in the tibolone group (15.7 +/- 9.2 vs 11.3 +/- 6.8, p < 0.001), while in the control group no difference was observed. There was a significant improvement of sexual function in the tibolone group in all domains: desire -- from 2.6 +/- 1.0 to 3.1 +/- 1.0 (p < 0.001); arousal -- from 2.3 +/- 1.8 to 3.4 +/- 1.1 (p < 0.001); lubrication - 2.6 +/- 2.1 and 3.5 +/- 1.4 (p < 0.05). The ability to reach orgasm increased (p < 0.001) and pain and discomfort during and after sexual intercourse significantly decreased (p < 0.01). These parameters did not change in the control group. Included results in appraisal table were inconsistent.
Quality of Evidence: Low

9. **<u>Tibolone vs. Hormone Therapy</u>:** Two RCTs were found comparing the effects of hormone therapy to tibolone. One RCT (Polisseni 2013), randomized patients into three groups: (1) daily treatment with 2.5mg tibolone (n=64), (2) 50mg calcium carbonate+200 IU vitamin D3 (Ca/Vit D3, n=54) or (3) 1mg oestradiol+0.5mg norethindrone acetate (E2/NETA, n=56) for 12 weeks. A total of 130 women in the following groups completed the study: tibolone (n=42), Ca/Vit D3 (n=44) and E2/NETA (n=44). An improved QoL based on the WHQ was observed at T0 (80.12+/-14.04, 77.73+/-15.3, 77.45+/-15.4) and T12 (57.0+/-15.5, 55.7+/-16.7, 58.4+/-12.6) for the tibolone, E2+NETA and Ca/Vit D3 groups, respectively (p values <0.05). The three groups

exhibited significantly different scores at T12 for sexual behaviour and vasomotor symptoms. The tibolone group exhibited better sexual function compared with the E2/NETA and Ca/Vit D3 groups (4.2+/-26, 5.6+/-2.8, 5.4+/-2.8, respectively, p values <0.05). LD-HT was superior to tibolone and Ca/Vit D3 treatment for improvements in vasomotor symptoms (3.2+/-1.5, 4.0+/-1.8, 4.3+/-2.0, respectively, p values <0.05). Adverse effects were few and mild. Another RCT (Ziaei 2010) allocated women into three groups. 2.5 mg tibolone + one Cal+D tablet (500 mg calcium and 200 IU vitamin D) daily intervention group; 0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone (CEE/MPA) + one Cal+D tablet daily intervention group; and one Cal+D tablet as the control group. The Greene Climacteric Scale (GCS) questionnaire was used to detect the efficacy of treatment on climacteric symptoms. Rosen's Female Sexual Function Index (FSFI) was used for sexual function evaluation. Sex hormone binding globulin (SHBG), free estradiol index (FEI) and free testosterone index (FTI) were measured before and after treatment. The women were followed up for 6 months. After treatment, all subscores in the GCS improved in the tibolone and CEE/MPA groups ($p < 0.01$), except the sexual subscore in the CEE/MPA group, compared with baseline. There were significant differences in the FSFI in the tibolone and CEE/MPA groups in comparison to the control group after treatment. Tibolone, in comparison to CEE/MPA, significantly lowered SHBG levels and increased the FTI and FEI and improved the desire, arousal and orgasm sexual domains of the FSFI ($p < 0.001$).
Quality of Evidence: Low

10. **Estrogen with Testosterone:** Two RCTs were found evaluating the effect of testosterone with estrogen. One RCT (Penteado 2008), randomized postmenopausal women into two groups, one, known as EP, received one tablet of equine estrogens 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg and one capsule of placebo; EP + A (n = 31) received one tablet of CEE 0.625 mg plus MPA 2.5 mg and one capsule of methyltestosterone 2.0 mg; The treatment period was 12 months. Statistical analysis gave a X^2 value of 11.551 (p=0.021), indicating a significant association between the reported improvement in the sexual energy level and the addition of methyltestosterone to hormone treatment. The second RCT (Raghunandan 2010), randomly divided participants into two groups and one control group. The women in study group 1 received local estrogen cream; study group 2 received local estrogen and testosterone cream; the control group received nonhormonal lubricant KY gel for 12 weeks. The urogenital and sexuality score, along with the vaginal health index and the vaginal maturation index (VMI), was calculated at the beginning of therapy and 12 weeks later. A decline in urogenital symptoms occurred in study group 1 (58%), study group 2 (62%), and the control group (25%). There was a significant difference in improvement between the study groups and the control group. However, the improvement seen in study groups 1 and 2 was found to be comparable.
Quality of Evidence: Low

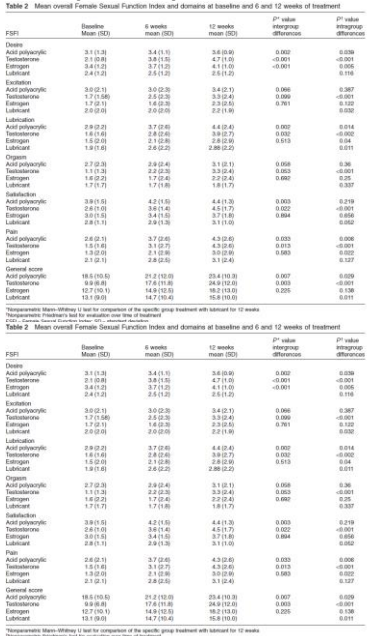
In conclusion, there is moderate to low quality of evidence to support the use of different types of hormone therapy for menopausal women with low libido. The majority of the modalities (Combined Hormone Therapy; Estrogen; Conjugated Estrogen; Conjugated Estrogen/Bazedoxifene; Fesoterodine and Estrogen; Estradiol; Tibolone; Tibolone vs. Hormone Therapy; and Estrogen with

Testosterone) were rated low due to inconsistency between study results and variation in treatment, and due to imprecision when studies included few patients and/or events. Additionally, the estrogen-progestogen therapy modality was rated as moderate overall.

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality
Modality: Hormonal Replacement Therapy; **Outcome:** Benefits						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 2 # of RCTs: 1 # of Non-Randomized Studies: 1						
Genazzani, A.R., et al., 2011, *Climacteric*	To evaluate the effects of different types of hormonal replacement therapy (HRT) on sexual function, frequency of sexual intercourse, and quality of relationship in early postmenopausal women.	RCT; Women with climacteric symptoms were uniformly randomized into three groups receiving either dehydroepiandrosterone (DHEA 10 mg) daily, or daily oral estradiol (1 mg) plus dihydrogesterone (5 mg), or daily oral tibolone (2.5 mg) for 12 months. Women who refused hormonal therapy were treated with oral vitamin D (400 IU). Efficacy was evaluated using the McCoy Female Sexuality Questionnaire before treatment and after 12 months. Women's hormonal profile was evaluated before treatment and after 3, 6 and 12 months.	48 healthy postmenopausal women aged 50-60 years	**The groups receiving DHEA or HRT reported a significant improvement in sexual function compared to baseline ($p < 0.001$ and $p < 0.01$, respectively)** using the McCoy total score. The quality of relationship was similar at baseline and after 3, 6 and 12 months of treatment. There were significant increases in the numbers of episodes of sexual intercourse in the previous 4 weeks in women treated with DHEA, HRT and tibolone in comparison with the baseline value ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). No changes in the McCoy score occurred in women receiving vitamin D.	Study Limitations = ☐ None ***RCTS*** ☒ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	
Tucker, P.E., et al., 2016, *Maturitas*	To investigate the effects of pre-operative menopausal status and HRT use on sexual outcomes following risk-reducing salpingo-oophorectomy (RRSO).	Cross-sectional Study; Data was collected via a questionnaire and serum test for testosterone and free androgen index (FAI). The questionnaire comprised demographic data and validated measures of sexual function, sexual distress, relationship satisfaction, body image, psychological stress, menopause quality of life and general quality of life.	119 women; 58% response rate	**HRT use reduced the rates of dyspareunia ($p=0.027$) and the severity of sexual menopausal symptoms ($p=0.030$). Androgen levels were not significantly associated with desire or arousal scores.**	***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

						Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Labrie, F., et al. (2014). *Journal of Sexual Medicine*	Investigate the influence of moderate/severe pain at sexual activity (dyspareunia) (MSD) at baseline on female sexual dysfunction (FSD) following prasterone administration	RCT. The effect of daily administration of prasterone (0, 3.25mg, 6.5mg or 13mg) for 12 weeks on FSD in women with or without MSD at baseline was evaluated	215 postmenopausal women	**Comparable benefits were observed in women not having MSD (n = 56) vs. those having MSD (n = 159). The benefits over placebo in prasterone-treated women for desire is improved at week 12 by 22% (P = 0.016), 51% (P = 0.0047), 31% (P = 0.2845) and 48% (P = 0.0072) in the placebo, 0.25%, 0.5% and 1.0% prasterone groups, respectively.**	Study Limitations = ☒ None ***RCTS*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*
Modality: Estrogen; **Outcome:** Benefits						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of Non-Randomized Studies: 1						
Nastri, C.O., et al., 2013,	To assess the effect of	Systematic Review	3 studies; 699 women	**For estrogens alone versus control, in symptomatic or early postmenopausal women the SMD**	Study Limitations = ☒ None ***Systematic Review***	

Cochrane Database of Systematic Reviews	hormone therapy (HT) on sexual function in perimenopausal and postmenopausal women			**and 95% CI were compatible with a small to moderate benefit in sexual function for the HT group (SMD 0.38, 95% CI 0.23 to 0.54, P < 0.00001, high-quality evidence).**	☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect
Fernandes, T., et al., 2014, *Journal of Sexual Medicine*	To evaluate female sexual function after using topic estrogen, testosterone, or polyacrylic acid as vaginal lubricants with K-Y jelly as a placebo lubricant	RCT; Postmenopausal women between 40 and 70 years of age were included with follow-up at the Menopause Clinic of the CAISM Unicamp. The women were randomized to treatment with topical vaginal estrogen, testosterone, polyacrylic acid, or oil lubricant alone, three times a week for a period of 12 weeks.	80 women; 20 allocated to estrogen intervention	**After 12 weeks of treatment, estrogen produced improvements in the FSFI domains of sexual desire, lubrication, satisfaction, reduced pain during intercourse, and total score compared with lubricant alone. (*P* < 0.001).** Table 2 Mean overall Female Sexual Function Index and domains at baseline and 6 and 12 weeks of treatment 	Study Limitations = ☒ None ***RCTS*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	
Setty, P., et al. (2016). *Menopause*	This study investigates the use and effects of vaginal	Comparative study. Three groups were compared: group 1, women who have remained on hormone therapy (HT)/estrogen therapy (ET); group 2, women	310 women. 159 remained on HT/ET (group 1), 43 resumed HT/ET after stopping for at least 6 months	**There was no statistically significant difference in sexual quality of life, dyspareunia, vaginal dryness, urinary tract infection, or married or married-like relationship across the**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria	Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate

	estrogen on quality of life and urogenital morbidity among women who stopped hormone therapy after the Women's Health Initiative and compares them with women who continued hormone therapy.	who have resumed HT/ET after stopping for at least 6 months, and group 3, women who have stopped HT/ET and have not resumed.	(group 2), and 108 women discontinued HT/ET altogether (group 3).	**three groups**. However, for group 3 and sexual quality of life in particular, those who used VE had higher scores on the sexual quality-of-life scale than those who did not use VE (P=0.007). **TABLE 5.** *Sexual QOL and vaginal symptoms results* Group 1 / Group 2 / Group 3[a] / P Sexual quality of life: 9.88 (3.59) / 9.80 (2.94) / 9.80 (3.14) / NS Dyspareunia[b]: 1.95 (1.3) / 2.63 (1.6) / 2.26 (1.4) / NS Vaginal dryness[b]: 1.65 (0.9) / 1.88 (1.0) / 1.98 (1.0) / NS Data are presented as mean (SD). NS, not significant. [a]Women who used vaginal estrogen had higher scores on the sexual quality-of-life scale compared with women who did not use vaginal estrogen ($P=0.007$; one-way analysis of variance controlling for age). [b]Across all 310 women, use of vaginal estrogen was most prevalent among those who reported dyspareunia (ever, $P=0.003$; present, $P=0.005$) and vaginal dryness (ever, $P=0.001$; present, $P=0.004$).	☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	☒ Low ☐ Very Low

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)

Modality: Conjugated Estrogen; **Outcome:** Benefits

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of RCTs: 2					
Freedman, M., et al., 2009, *Menopause*	To evaluate low-dose synthetic conjugated estrogens A (SCE-A) cream administered twice weekly for the treatment of moderate to severe	RCT; Women with symptoms of VVA were treated with either 1 g SCE-A cream or matching placebo for a period of up to 12 weeks. Participants had to have a vaginal pH of greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and at least one of five symptoms of VVA (dryness, soreness, irritation, pain with intercourse, and bleeding after intercourse) that was moderate or severe in intensity. Women had to select one moderate or	305 women, 150 in treatment group and 155 in placebo group	Efficacy was assessed at 2, 3, 4, 8, and 12 weeks and included the change from baseline in the severity of the most bothersome symptom (MBS), maturation index, and pH. Most women identified vaginal dryness as the MBS (48%) followed by pain with intercourse (31.3%). **A statistically significant increase in the maturation index (P < 0.0001) and significant decreases in pH (P < 0.0001) and severity of the MBS (P < 0.0001) were observed for those treated with SCE-A vaginal cream compared with placebo.**	Study Limitations = ☒ None ***RCTS*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline

Lower Quality Rating if:
☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

	vulvovaginal atrophy (VVA) in a symptomatic postmenopausal population	severe symptom as the most bothersome.				☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*
Gast, M.J., et al., 2009, Menopause	To evaluate the effects of combined vaginal and oral low-dose estrogen plus progestogen therapy (EPT) on the frequency and severity of dyspareunia, sexual function, and quality of life in recently postmenopausal women	RCT; Women were randomized to one of two treatment groups: group A received estrogen plus progestogen therapy (EPT) with daily oral low-dose CE (PREMARIN)/medroxyprogesterone acetate (MPA) (0.45 mg CE/1.5 mg MPA) for six 28-day cycles along with initial vaginal priming with 1 g CE(PREMARIN) cream (0.625 mg CE/g) intravaginally for the first 6 weeks. Group B received an oral placebo tablet daily for six 28-day cycles along with 1 g placebo cream, intravaginally, for the first 6 weeks.Efficacy was evaluated using the McCoy Female Sexuality Questionnaire, self-reported daily diary cards, the Brief Index of Sexual Functioning-Women (BISF-W), and the Women's Health Questionnaire.	285 healthy, sexually active postmenopausal women aged 45 to 65 years 144 in EPT group and 141 in placebo group	The EPT group had a significant decrease in the frequency of dyspareunia compared with baseline and placebo in an analysis of responses to the McCoy Female Sexuality Questionnaire. **Also, EPT was associated with a significant improvement in a woman's level of sexual interest, frequency of orgasm, and pleasure of orgasm (*P* < 0.05)**. There was no effect of EPT use on coital frequency. The EPT group had significant improvement in receptivity/initiation and relationship satisfaction (P < 0.05), although not in other BISF-W domains, versus placebo (BISF-W analysis) and significant improvement versus placebo on most Women's Health Questionnaire response (P < 0.05),	Study Limitations = ☐ None RCTS ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline	☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations,*
Modality: Conjugated estrogen/bazedoxifene; **Outcome:** Benefits						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 3 # of Systematic Reviews: 1 # of RCTs: 1 # of Non-Randomized Studies: 1						
Nastri, C.O., et al.,	To assess	Systematic Review	2 studies;	**In the comparison of selective**	Study Limitations =	

2013, *Cochrane Database of Systematic Reviews*	the effect of hormone therapy (HT) on sexual function in perimenopausal and postmenopausal women		498 women	**estrogen receptor modulators (SERMs) (such as raloxifene and bazedoxifene) versus control, for symptomatic or early postmenopausal women the observed effect was compatible with no effect to a moderate benefit for sexual function in the HT group (SMD 0.23, 95% CI -0.04 to 0.50, P = 0.09, low-quality evidence).** In unselected postmenopausal women, the 95% CI was compatible with small harm to a small benefit (SMD 0.04, 95% CI -0.20 to 0.29, P = 0.72, low-quality evidence).	☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	*interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies
Bachmann, G., et al., 2010, *Climacteric*	To evaluate the effects of the tissue selective estrogen complex (TSEC) pairing bazedoxifene (BZA) with conjugated estrogens (CE) on sexual function and quality of life in postmenopausal women	RCT; Postmenopausal, non-hysterectomized women with symptoms of moderate to severe vulvar/vaginal atrophy were randomized to once-daily treatment with BZA 20 mg/CE 0.45 or 0.625 mg, BZA 20 mg, or placebo for a 12-week study. The Arizona Sexual Experiences (ASEX) Scale, Menopause-Specific Quality of Life (MENQOL) questionnaire, and Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ) were secondary measures used to assess the effects of BZA/CE on sexual function, menopausal symptoms, and satisfaction with treatment, respectively.	652 women	At week 12, both BZA/CE doses were associated with significant improvement in ease of lubrication score from baseline compared with placebo ($p < 0.05$) on the ASEX scale, although there was no difference in the change in total score. **The MENQOL questionnaire results at week 12 showed significant improvements in vasomotor function, sexual function and total scores with both BZA/CE doses vs. placebo or BZA 20 mg ($p < 0.001$).** The MS-TSQ results showed that BZA/CE-treated subjects reported significantly greater overall satisfaction with treatment, as well as satisfaction with control of hot flushes during the day and night, effect on quality of sleep, and effect on mood or emotions, compared with subjects treated with placebo or BZA 20 mg (all $p < 0.05$).	Study Limitations = ☐ None ***RCTS*** ☒ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	
Abraham, L., et al., 2014, *Maturitas*	Describe the effects of conjugated estrogens/bazedoxifene (CE/BZA) on menopause-specific quality of life (MSQOL)	Retrospective Study; CE/BZA was evaluated in a series of multicenter, randomized, double-blind, placebo-controlled, and active-controlled phase 3 trials known as the SMART trials, which have been previously published. Healthy, non-hysterectomized postmenopausal women with	6,426 women	Significant improvements compared with placebo were found with both CE/BZA doses in MENQOL vasomotor domain (-0.61 to -2.23 over 3-24 months) and total scores (-0.24 to -0.94) in the general and symptomatic VMS/VVA populations. **Significant improvement compared with placebo in sexual domain (-0.11 to -0.72) was observed with the higher**	Study Limitations = ☐ None ***Non-Randomized Studies*** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately	

	across different patient population types in phase 3 clinical trials.	symptomatic VMS or vulvar-vaginal atrophy (VVA) and general postmenopausal women were included in the study (eligible regardless of symptoms). Menopause-specific Quality of Life (MENQOL) questionnaire total and domain scores for CE 0.625 mg/BZA 20mg and CE 0.45 mg/BZA 20mg were evaluated and compared with established thresholds for clinically important differences (CID).		**dosage for all populations, and with the lower dosage in the VVA (-0.71 at month 3) and general populations (-0.4 at months 12 and 24).** Improvements in vasomotor domain exceeded the CID with both doses in symptomatic VMS populations and with the higher dosage in women with symptomatic VVA; for total MENQOL, the CID was exceeded with the higher dose in symptomatic VMS populations.	control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)						Lower Quality Rating if:
Outcome: Fesoterodine and Estrogen; **Outcome:** Benefits						☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have*
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of RCTs: 1						
Chughtai, B., et al., 2016, *Post reproductive health*	To investigate the combination effect of anti-muscarinic medication and topical vaginal estrogen in the treatment of overactive bladder (OAB) and female sexual dysfunction in postmenopausal women	RCT: Subjects with a history of overactive bladder symptoms for at least 3 months, who met the entry criteria were randomized into two groups: (1) fesoterodine (Toviaz, Pfizer, NY) with topical vaginal estrogen (Premarin, Pfizer, NY) once daily or (2) fesoterodine once daily alone. If 4 mg fesoterodine was tolerated at 1-week, the dose was increased to 8 mg. Primary endpoints were improvement in OAB symptom severity (Overactive Bladder Questionnaire, OAB-Q SF), improvement in OAB health-related quality of life (HRQL) (OAB-Q SF), and sexual function (Sexual Quality of Life-Female, SQOL-F) after 12 weeks. Secondary endpoint	23 female subjects	**After 12-weeks, the combination group had a significant improvement in OAB symptom severity (p = 0.006), HRQL (p = 0.029), and SQOL-F (0.0003).** The fesoterodine alone group also had significant improvement in OAB symptom severity (p < 0.0001), HRQL (p = 0.0002), and SQOL-F (p = 0.02). When compared directly to the fesoterodine alone group, the combination group after 12-weeks had a reduced OAB symptom severity (10 versus 23.3; p = 0.35), higher HRQL (96.9 versus 84.6; p = 0.75), and higher SQOL-F (99 versus 81; p = 0.098). The total number of micturitions over 3 d was significantly reduced in the combination group (45-26, p = 0.03) between baseline and 12-weeks.	Study Limitations = ☐ None ***RCTS*** ☒ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline	

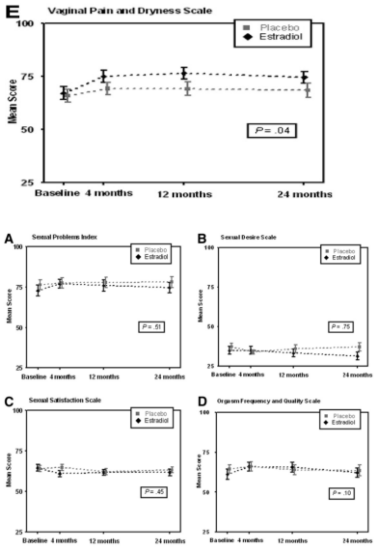
		was change in total number of micturitions.				*wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)						<u>Lower Quality Rating if:</u> ☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect
Modality: Estrogen-progestogen therapy; **Outcome:** Benefits						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 2 # of Systematic Reviews: 1 # of RCTs: 1						
Nastri, C.O., et al., 2013, *Cochrane Database of Systematic*	To assess the effect of hormone therapy (HT) on sexual	Systematic Review	1 study, 335 women	**For estrogens combined with progestogens versus control, in symptomatic or early postmenopausal women the 95% CI was compatible with a small to moderate benefit for sexual function**	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or	

Reviews	function in perimenopausal and postmenopausal women			**in the HT group (SMD 0.42, 95% CI 0.19 to 0.64, P = 0.0003, moderate-quality evidence).**	exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	*(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low
Fonseca, A.M., et al., 2007, *Clinical Drug Investigation*	To evaluate the effects of monophasic estrogen-progestogen therapy on the sexuality and climacteric symptoms of postmenopausal women	RCT; Carried out over a total of 12 consecutive months in women with an intact uterus who had no contraindications to hormone therapy. Patients received 17beta-estradiol 2mg in combination with norethisterone acetate 1mg (Cliane) daily for 6 months in Group A or one placebo tablet daily for 6 months in Group B. The tablets were identical in appearance. After 6 months, the groups were crossed over and the patients were followed up for another 6 months. The groups were homogenous with respect to age, height, bodyweight, body mass index and race. For the statistical analysis, the group receiving hormone therapy was referred to as group A and the placebo group was designated group B, irrespective of the placebo/hormone therapy sequence.	40 postmenopausal women	**In group A there were fewer hot flashes (F=22.85, p<0.01) and an improvement in sexual interest (F=5.55, p<0.05). The sequence in which the medication was received resulted in a statistically significant difference with respect to dyspareunia (F=9.65, p<0.01) and satisfaction with the duration of penetration (F=6.58, p<0.05).** In the intrapatient analysis of variation with respect to orgasmic capability and the presence of dialogue with partner regarding the couple's sexual life, whether the placebo was taken prior to or following hormone therapy was significant (F=17.12, p<0.001 and F=7.10, p<0.05, respectively).	Study Limitations = ☐ None ***RCTS*** ☐ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)

Modality: Estradiol; **Outcome:** Benefits

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of RCTs: 2					
Huang, A., et al. (2008). *American Journal of Obstetrics & Gynecology*	To examine the effect of ultralow-dose transdermal estradiol on sexual function in postmenopausal women.	RCT. Participants at each center were allocated in equal proportions to treatment or placebo in randomly permuted blocks of size 4. Treatment consisted of a 3.25 cm2 patch releasing 0.014 mg of estradiol per day or an identical placebo patch applied weekly. Participants, investigators, and outcome assessors were blinded to treatment assignment, and no unblinding occurred during the trial.	417 women aged 60 to 80 years who had an intact uterus but who had not had a menstrual period in at least 5 years.	**Women randomly assigned to estradiol had a 4.3 point greater improvement in the vaginal pain/dryness domain relative to placebo (95% CI = 0.3-8.4, P = .04). No significant differences in frequency of sexual activity or other sexual function domains (desire, satisfaction, problems, or orgasm) were observed between treatment groups (P ≥ .10 for all).**  	Study Limitations = ☒ None ***RCTS*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

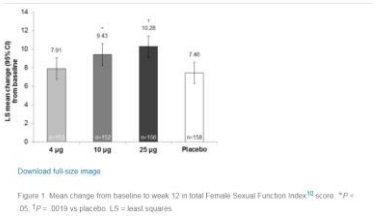
☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

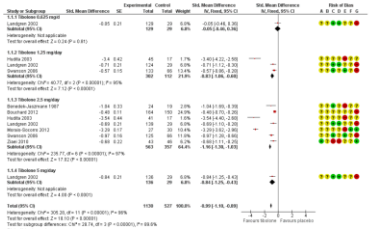
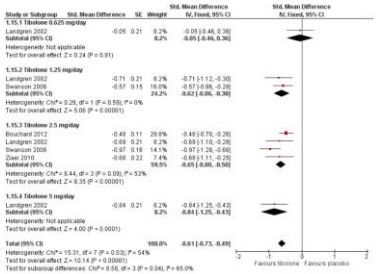
☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

Kingsberg, S. A., et al. (2016). *Journal of Sexual Medicine*	To evaluate the effect of TX-004HR (estradiol vaginal drug) on female sexual dysfunction in postmenopausal women with vulvar and vaginal atrophy (VVA).	RCT. The study compared the effects of 12-week treatment with TX-004HR (4, 10, or 25 µg) with placebo in postmenopausal women (40-75 years old) with VVA and a most bothersome symptom of moderate to severe dyspareunia.	704 women	**All three TX-004HR doses increased the baseline total FSFI score after 12 weeks, with 10 µg (P < .05) and 25 µg (P = .0019) having a significantly greater effect than placebo. A similar trend was observed for the individual FSFI domains, with 10 and 25 µg significantly improving baselines scores for pain and lubrication at 12 weeks (P ≤ .015 for all vs placebo). Changes from baseline to week 12 in arousal (P = .0085) and satisfaction (P = .0073) were significantly greater for TX-004HR 25 µg vs placebo. All three TX-004HR doses were comparable to placebo in their effect on desire and orgasm.**  Download full-size image Figure 1. Mean change from baseline to week 12 in total Female Sexual Function Index[10] score. *P < .05. †P = .0019 vs placebo. LS = least squares.	Study Limitations = ☒ None ***RCTS*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect
Modality: Tibolone; **Outcome:** Benefits						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 5 # of Systematic Reviews: 2 # of RCTs: 2 # of Non-Randomized Studies: 1						
Nastri, C.O., et al., 2013, *Cochrane Database of Systematic Reviews*	To assess the effect of hormone therapy (HT) on sexual function in	Systematic Review	3 studies; 1025 women	**For tibolone versus control, in symptomatic or early postmenopausal women the 95% CI was compatible with no effect to a small benefit for sexual function in the HT group (SMD 0.13, 95% CI 0.00 to 0.26, P = 0.05, low-quality**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive	

	perimenopausal and postmenopausal women			**evidence). In unselected postmenopausal women, the 95% CI was compatible with no effect to a moderate benefit (SMD 0.38, 95% CI 0.04 to 0.71, P = 0.03, low-quality evidence).**	☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	*(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Formoso, G., et al. (2016) *Cochrane Database of Systematic Reviews*	To evaluate the effectiveness and safety of tibolone for treatment of postmenopausal and perimenopausal women.	Systematic review.	16 RCTs; 6438 women	**Vasomotor Symptoms: Tibolone was more effective than placebo** (standard mean difference (SMD) -0.99, 95% confidence interval (CI) -1.10 to -0.89; seven RCTs; 1657 women; moderate-quality evidence), **but removing trials at high risk of attrition bias attenuated this effect (SMD -0.61, 95% CI -0.73 to -0.49; odds ratio (OR) 0.33, 85% CI 0.27 to 0.41). This suggests that if 67% of women taking placebo experience vasomotor symptoms, between 35% and 45% of women taking tibolone will do so.** **Figure 4. Forest plot of comparison: 1 Tibolone versus placebo, outcome: 1.1 Vasomotor symptoms.**  **Figure 5. Forest plot of comparison: 1 Tibolone versus placebo, outcome: 1.15 Sensitivity analysis - Vasomotor symptoms without trials with high risk of attrition bias.** 	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	

				Unscheduled bleeding vs combined hormone therapy: Tibolone was associated with a lower rate of bleeding (OR 0.32, 95% CI 0.24 to 0.41; 16 RCTs; 6438 women). This suggests that if 47% of women taking combined HT experience unscheduled bleeding, between 18% and 27% of women taking tibolone will do so.		
Kamenov, Z. A., et al. (2007). *Folia Medica*	The aim of the study was to assess the effect of tibolone on climacteric symptoms and sexuality in late postmenopausal but still symptomatic women	A six-month prospective study was conducted of two groups of clinically healthy postmenopausal women: a control group and a tibolone group. The Kupperman menopausal index (KI) was calculated for both groups at baseline and at six months. Sexual function was assessed by the Female Sexual Function Index (FSFI) questionnaire at the beginning and at the end of the study. The FSFI comprised five main domains: desire, arousal, lubrication, orgasm and pain. Satisfaction and a total score were also recorded.	40 women	The results showed that during the observation period **KI decreased significantly in the tibolone group (15.7 +/- 9.2 vs 11.3 +/- 6.8, p < 0.001),** while in the control group no difference was observed. There was a **significant improvement of sexual function in the tibolone group in all domains: desire -- from 2.6 +/- 1.0 to 3.1 +/- 1.0 (p < 0.001); arousal -- from 2.3 +/- 1.8 to 3.4 +/- 1.1 (p < 0.001); lubrication - 2.6 +/- 2.1 and 3.5 +/- 1.4 (p < 0.05). The ability to reach orgasm increased (p < 0.001) and pain and discomfort during and after sexual intercourse significantly decreased (p < 0.01).** These parameters did not change in the control group.	Study Limitations = ☐ None ***Non-Randomized Studies*** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Nijland, E. A., et al. (2007). *Maturitas*	To compare the effects of tibolone and raloxifene on health-related quality of life, sexuality and	RCT. The women were randomized to treatment with oral tibolone 1.25 mg or raloxifene 60 mg once daily for 2 years.	308 osteopenic women	*Health-related quality of life*: **In the raloxifene group, the WHQ vasomotor symptom domain showed consistently higher scores than in the tibolone group reflecting a worsening of vasomotor symptoms in the raloxifene group**.	Study Limitations = ☐ None ***RCTS*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT	

	vaginal atrophy.			The differences were statistically significant at week 12 (p = 0.005), week 24 (p = 0.001) and week 52 (p = 0.002). **Other domains showing statistically significant differences in favor of the tibolone group included depressed mood** at week 24 (p = 0.016) and week 104 (p < 0.001), **sexual behavior** at week 52 (p = 0.006) and week 104 (p = 0.011), **somatic symptoms** at week 52 (p = 0.048) and **attractiveness** at week 12 (p = 0.04). **There were no statistically significant advantages for raloxifene on any of the subscales.** *Sexual Function:* **there was little to no difference between the tibolone and raloxifene group in mean and median scores for the 4 domains (sexual interest, sex with partner, orgasm and vaginal lubrication) and the global score of the McCoy female sexuality questionnaire, short form at any of the post-baseline visits.** *Vaginal Atrophy:* **VA was improved by tibolone, but remained unchanged in the raloxifene group. The increase from baseline in both KI and VM was statistically significantly (p < 0.0001) greater with tibolone than with raloxifene after 52 and 104 weeks.**	☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline	
Nijland, E. A., et al. (2008). *Journal of Sexual Medicine*	To compare the efficacy on sexual function of tibolone 2.5 mg to continuous combined transdermal	RCT. Women were treated with E2 (50 mg)/NETA (140 mg) in the form of a twice weekly patch plus a daily placebo tablet or tibolone 2.5 mg as a daily tablet with a twice weekly placebo patch. Sexual function was assessed with the FSFI at baseline,	403 naturally postmenopausal women	*FSFI:* **The greater increase in this score with tibolone compared with E2 /NETA approached statistical significance in the ITT analysis (P = 0.065***).* *FSDS:* There was a statistically significant reduction in sexuality-related	Study Limitations = ☐ None ***RCTS*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of	

	estradiol (E2)/norethisterone acetate (NETA) (50 microg/140 microg) in naturally postmenopausal women with sexual dysfunction.	week 12, and week 24. The outcomes of the Female Sexual Distress Scale (FSDS) and the frequency of satisfying sexual events (daily diaries) were secondary end points.		personal distress in both treatment groups when compared to baseline (P < 0.001 for both groups). **No differences were observed between the groups.** *SSE:* increased from three to four times per 28 days at week 24 (P < 0.001 from baseline for both groups), **with no difference between groups**.	measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline	

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)						Lower Quality Rating if:
Modality: Hormone Therapy vs Tibolone; **Outcome:** Benefits						☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 2 # of RCTs: 2						
Polisseni, A.F., et al., 2013, *Maturitas*	To compare the effects of a continuous-combined regimen of low-dose hormone therapy (LD-HT) versus tibolone and supplemental calcium/vitamin D3 (control) on quality of life (QoL) in symptomatic postmenopausal women	RCT; The patients were randomised into three groups: (1) daily treatment with 2.5mg tibolone (n=64), (2) 50mg calcium carbonate+200 IU vitamin D3 (Ca/Vit D3, n=54) or (3) 1mg oestradiol+0.5mg norethindrone acetate (E2/NETA, n=56) for 12 weeks. The primary outcome was the evaluation of QoL using the Women's Health Questionnaire (WHQ) in all subjects at baseline and after 4, 8 and 12 weeks of treatment.	174 postmenopausal women under 60 years old	A total of 130 women in the following groups completed the study: tibolone (n=42), Ca/Vit D3 (n=44) and E2/NETA (n=44). **An improved QoL based on the WHQ was observed at T0 (80.12+/-14.04, 77.73+/-15.3, 77.45+/-15.4) and T12 (57.0+/-15.5, 55.7+/-16.7, 58.4+/-12.6) for the tibolone, E2+NETA and Ca/Vit D3 groups, respectively (p values <0.05).** The three groups exhibited significantly different scores at T12 for sexual behaviour and vasomotor symptoms. **The tibolone group exhibited better sexual function compared with the E2/NETA and Ca/Vit D3 groups (4.2+/-26, 5.6+/-2.8, 5.4+/-2.8, respectively, p values <0.05). LD-HT was superior to tibolone and Ca/Vit D3 treatment for improvements in vasomotor symptoms (3.2+/-1.5, 4.0+/-1.8, 4.3+/-2.0, respectively, p values <0.05). Adverse effects were few and mild.**	Study Limitations = ☐ None ***RCTS*** ☐ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline	
Ziaei, S., et al., 2010,	To compare the effects of tibolone with those of	RCT; Women were allocated into three groups. 2.5 mg tibolone + one Cal+D tablet (500 mg calcium and 200 IU vitamin D)	140 postmenopausal women; 47 women received 2.5 mg tibolone + one Cal+D	After treatment, all subscores in the GCS improved in the tibolone and CEE/MPA groups (p < 0.01), except the sexual subscore in the CEE/MPA	Study Limitations = ☐ None ***RCTS*** ☒ Lack of blinding	

Climacteric	conventional hormone replacement therapy on climacteric symptoms and sexual function in postmenopausal women.	daily intervention group; 0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone (CEE/MPA) + one Cal+D tablet daily intervention group; and one Cal+D tablet as the control group. The Greene Climacteric Scale (GCS) questionnaire was used to detect the efficacy of treatment on climacteric symptoms. Rosen's Female Sexual Function Index (FSFI) was used for sexual function evaluation. Sex hormone binding globulin (SHBG), free estradiol index (FEI) and free testosterone index (FTI) were measured before and after treatment. The women were followed up for 6 months	tablet (500 mg calcium and 200 IU vitamin D) daily; 46 women received 0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone (CEE/MPA) + one Cal+D tablet daily; and 47 women received only one Cal+D tablet as the control group.	group, compared with baseline. **There were significant differences in the FSFI in the tibolone and CEE/MPA groups in comparison to the control group after treatment. Tibolone, in comparison to CEE/MPA, significantly lowered SHBG levels and increased the FTI and FEI and improved the desire, arousal and orgasm sexual domains of the FSFI (p < 0.001).**	☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	*(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

PICO Question: In treatment of low libido in menopausal women, what are the benefits of traditional hormone therapy (estrogen or estrogen plus progestin)

Modality: Estrogen with Testosterone; **Outcome:** Benefits

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	Lower Quality Rating if:
Total # of Studies: 2 # of RCTs: 2						
Penteado, S. R., et al. (2008). *Climacteric*	To evaluate the effect of the addition of methyltestosterone to estrogen and progestogen therapy on postmenopausal sexual energy and	RCT. Postmenopausal women were randomly divided into two groups: EP (n = 29) received one tablet of equine estrogens (CEE) 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg and one capsule of placebo; EP + A (n = 31) received one tablet of CEE 0.625 mg plus MPA 2.5 mg and one capsule of methyltestosterone 2.0	60 women	**Statistical analysis gave a X^2 value of 11.551 (p=0.021), indicating a significant association between the reported improvement in the sexual energy level and the addition of methyltestosterone to hormone treatment**	Study Limitations = ☐ None ***RCTS*** ☐ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important	☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention,*

	orgasm.	mg; The treatment period was 12 months.		Table 3 Sexual parameters analyzed during the study EP (n = 24) / EP + A (n = 27) Baseline / 12 months / Baseline / 12 months Masturbation: 4.79 ± 7.58 / 3.21 ± 5.66 / 3.37 ± 8.32 / 5.26 ± 8.77 Orgasm: 7.71 ± 11.80 / 23.71 ± 46.31* / 3.70 ± 4.28 / 20.33 ± 19.72* Sexual intercourse: 16.25 ± 12.16 / 24.41 ± 20.19* / 18.56 ± 12.92 / 27.00 ± 22.16* Sexual desire: 4.60 ± 4.36 / 7.24 ± 3.64* / 3.70 ± 3.72 / 9.04 ± 2.70* Sexual excitation: 4.84 ± 4.22 / 7.32 ± 3.63* / 3.63 ± 3.76 / 9.00 ± 2.77* Vaginal dryness (%): 67 / 21† / 81 / 19‡ EP, conjugated estrogens 0.625 mg + medroxyprogesterone acetate 2.5 mg + placebo; EP + A, conjugated estrogens 0.625 mg + medroxyprogesterone acetate 2.5 mg + methyltestosterone 2.0 mg *p < 0.001 compared to baseline; †p < 0.01, χ² = 10.24 compared to baseline in EP group; ‡p < 0.01, χ² = 21.41 compared to baseline in EP + A group	prognostic factors at baseline	*comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*
Raghunandan, C., et al. (2010). *Journal of Sexual Medicine*	To study the effects of local estrogen with or without local testosterone on urogenital and sexual health in postmenopausal women.	RCT. postmenopausal women symptomatic for urogenital atrophy and sexual dysfunction were randomly divided into two study groups and one control group. The women in study group 1 received local estrogen cream; study group 2 received local estrogen and testosterone cream; the control group received nonhormonal lubricant KY gel for 12 weeks. The urogenital and sexuality score, along with the vaginal health index and the vaginal maturation index (VMI), was calculated at the beginning of therapy and 12 weeks later	75 women	**A decline in urogenital symptoms occurred in study group 1 (58%), study group 2 (62%), and the control group (25%). There was a significant difference in improvement between the study groups and the control group. However, the improvement seen in study groups 1 and 2 was found to be comparable** Table 2 Comparative effect of local estrogen, estrogen and testosterone and non-hormonal gel on vulvovaginal health and sexual dysfunction Study group I / Study group II / Contro group / P Value Urogenital score: 0 weeks: 7.76 ± 1.98 / 6.48 ± 2.29 / 6.64 ± 1.66 / >0.05* 12 weeks: 3.20 ± 1.67 / 2.44 ± 1.80 / 5.00 ± 1.28 / <0.01** Mean change: 58.7 / 62.3 / 24.7 Sexuality score: 0 weeks: 4.24 ± 1.51 / 4.32 ± 1.41 / 4.92 ± 1.53 / >0.05* 12 weeks: 6.04 ± 1.61 / 10.68 ± 2.69 / 5.84 ± 1.37 / <0.01** Mean change: 42.4 / 147.3 / 18.6 VHI: 0 weeks: 13.12 ± 2.52 / 13.24 ± 1.61 / 13.32 ± 2.32 / >0.05* 12 weeks: 18.96 ± 2.32 / 20.12 ± 1.72 / 15.84 ± 2.39 / <0.01** Mean change: 44.5 / 51.9 / 18.9 VMI: 0 weeks: 46.10 ± 5.26 / 45.74 ± 6.16 / 46.78 ± 5.68 / >0.05* 12 weeks: 52.98 ± 5.84 / 53.2 ± 5.68 / 47.98 ± 5.77 / <0.01** Mean change: 15 / 16.3 / 2.5 *Insignificant, **Highly significant VMI = vaginal maturation index	Study Limitations = ☐ None ***RCTS*** ☒ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

Guideline Recommendations:

Seven guidelines included recommendations on hormone therapy therapies for menopausal women, which are outlined below.

In 2017, **The North American Menopause Society** released the following hormone therapy position statement:

> Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture. The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing or discontinuing HT.
>
> For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture. For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be for documented indications such as persistent VMS or bone loss, with shared decision making and periodic reevaluation. For bothersome GSM symptoms not relieved with over-the-counter therapies and without indications for use of systemic HT, low-dose vaginal estrogen therapy or other therapies are recommended.

In 2017, **the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)** Position Statement updated the menopause clinical practice guidelines published in 2011:

<u>New recommendations in this position statement include:</u>

1. Recommendation: the use of menopausal hormone therapy in symptomatic postmenopausal women should be based on consideration of all risk factors for cardiovascular disease, age, and time from menopause.
2. Recommendation: the use of transdermal as compared with oral estrogen preparations may be considered less likely to produce thrombotic risk and perhaps the risk of stroke and coronary artery disease.
3. Recommendation: when the use of progesterone is necessary, micronized progesterone is considered the safer alternative.
4. Recommendation: in symptomatic menopausal women who are at significant risk from the use of hormone replacement therapy, the use of selective serotonin re-uptake inhibitors and possibly other nonhormonal agents may offer significant symptom relief.

5. Recommendation: AACE does not recommend use of bioidentical hormone therapy.
6. Recommendation: AACE fully supports the recommendations of the Comité de l'Évolution des Pratiques en Oncologie regarding the management of menopause in women with breast cancer.
7. Recommendation: HRT is not recommended for the prevention of diabetes.
8. Recommendation: In women with previously diagnosed diabetes, the use of HRT should be individualized, taking in to account age, metabolic, and cardiovascular risk factors.

The **American Family Physician** in 2016 stated the following recommendations:

SORT: KEY RECOMMENDATIONS FOR PRACTICE

CLINICAL RECOMMENDATION	*EVIDENCE RATING*	*REFERENCES*
Combined estrogen/progestogen therapy, but not estrogen alone, increases the risk of breast cancer after three to five years of use.	B	3
Systemic estrogen, alone or in combination with a progestogen, is the most effective therapy for menopausal hot flashes, and is approved by the U.S. Food and Drug Administration for this indication.	A	9
Because of the potential risks with long-term use of hormone therapy, clinicians should prescribe the lowest effective dosage for the shortest duration necessary to improve symptoms.	C	8, 12
There is no high-quality, consistent evidence that black cohosh, botanical products, omega-3 fatty acid supplements, or lifestyle modification alleviates hot flashes.	B	19–21
The decision to continue combined hormone therapy for more than three to five years should be made after reviewing the risks, benefits, and symptoms with the patient.	C	12
Effective nonhormonal therapies for genitourinary syndrome of menopause include vaginal moisturizers and oral ospemifene (Osphena).	B	31, 32

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

The United Kingdom's National Institute for Health and Care Excellence (NICE)'s **National Collaborating Centre for Women's and Children's Health** in 2015 recommended the following for hormone therapies:

Give information to menopausal women and their family members or carers (as appropriate) about the following types of treatment for menopausal symptoms:

- Hormonal, for example hormone replacement therapy (HRT)
- Non-hormonal, for example clonidine
- Non-pharmaceutical, for example cognitive behavioral therapy (CBT)

Give information on menopause in different ways to help encourage women to discuss their symptoms and needs.

Give information about contraception to women who are in the perimenopausal and postmenopausal phase. See guidance from

the Faculty of Sexual & Reproductive Healthcare (FSRH) on Contraception for women aged over 40 years .

Offer women who are likely to go through menopause as a result of medical or surgical treatment (including women with cancer, at high risk of hormone-sensitive cancer or having gynecological surgery) support and:

- Information about menopause and fertility before they have their treatment
- Referral to a healthcare professional with expertise in menopause

Altered Sexual Function

Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective. (At the time of publication [November 2015], testosterone did not have a UK marketing authorization for this indication in women. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

Starting and Stopping HRT

Explain to women with a uterus that unscheduled vaginal bleeding is a common side effect of HRT within the first 3 months of treatment but should be reported at the 3-month review appointment, or promptly if it occurs after the first 3 months (see recommendations on endometrial cancer in the NGC summary of the NICE guideline Suspected cancer: recognition and referral).

Offer women who are stopping HRT a choice of gradually reducing or immediately stopping treatment.

Explain to women that:

- Gradually reducing HRT may limit recurrence of symptoms in the short term
- Gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term

Long-term Benefits and Risks of Hormone Replacement Therapy

Venous Thromboembolism

Explain to women that:

The risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk

The risk of VTE associated with HRT is greater for oral than transdermal preparations

The risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk

Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a body mass index (BMI) over 30 kg/m2.

Consider referring menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

Cardiovascular Disease

Ensure that menopausal women and healthcare professionals involved in their care understand that HRT:

Does not increase cardiovascular disease risk when started in women aged under 60 years

Does not affect the risk of dying from cardiovascular disease

Be aware that the presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed.

The baseline risk of coronary heart disease and stroke for women around menopausal age varies from one woman to another according to the presence of cardiovascular risk factors

HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease

HRT with oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease

Explain to women that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke. Also explain that the baseline population risk of stroke in women aged under 60 years is very low (see Table 2 in the original guideline document).

Type 2 Diabetes

Explain to women that taking HRT (either orally or transdermally) is not associated with an increased risk of developing type 2 diabetes.

Ensure that women with type 2 diabetes and all healthcare professionals involved in their care are aware that HRT is not generally associated with an adverse effect on blood glucose control.

Consider HRT for menopausal symptoms in women with type 2 diabetes after taking comorbidities into account and seeking specialist advice if needed.

Breast Cancer

The baseline risk of breast cancer for women around menopausal age varies from one woman to another according to the presence of underlying risk factors

HRT with oestrogen alone is associated with little or no change in the risk of breast cancer

HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer

Any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT

Osteoporosis

Give women advice on bone health and discuss these issues at review appointments (see the NGC summary of the NICE guideline Osteoporosis: assessing the risk of fragility fracture).

Using Table 4 in the original guideline document, explain to women that the baseline population risk of fragility fracture for women around menopausal age in the UK is low and varies from one woman to another.

Using Table 4 in the original guideline document, explain to women that their risk of fragility fracture is decreased while taking HRT and that this benefit:

Is maintained during treatment but decreases once treatment stops

May continue for longer in women who take HRT for longer

Dementia

Explain to menopausal women that the likelihood of HRT affecting their risk of dementia is unknown.

Loss of Muscle Mass and Strength

Explain to women that:

There is limited evidence suggesting that HRT may improve muscle mass and strength

Muscle mass and strength is maintained through, and is important for, activities of daily living

In 2015, **The Endocrine Society** provided the following recommendations:

3.0 Hormone therapy for menopausal symptom relief

3.1 Estrogen and progestogen therapy

3.1a For menopausal women < 60 years of age or < 10 years past menopause with bothersome VMS (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take menopausal hormone therapy (MHT), we suggest initiating estrogen therapy (ET) for those without a uterus and estrogen plus progestogen therapy (EPT) for those with a uterus. (2|⊕⊕○○)

Cardiovascular risk

3.1b For women < age 60 or < 10 years past menopause onset considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of cardiovascular disease (CVD) and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|⊕⊕○○)

3.1c For women at high risk of CVD, we suggest initiating nonhormonal therapies to alleviate bothersome VMS (with or without climacteric symptoms) over MHT. (2|⊕⊕○○)

3.1d For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus, because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. (2|⊕⊕○○)

Venous thromboembolic events

3.1e For women at increased risk of venous thromboembolism (VTE) who request MHT, we recommend a nonoral route of ET at the lowest effective dose, if not contraindicated (1|⊕⊕○○); for women with a uterus, we recommend a progestogen (for example, progesterone and dydrogestone) that is neutral on coagulation parameters. (1|⊕⊕⊕○)

Breast cancer

3.1f For women considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|⊕⊕○○)

3.1g For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, we suggest nonhormonal therapies over MHT to alleviate bothersome VMS. (2|⊕⊕○○)

Tailoring MHT

3.1h We suggest a shared decision-making approach to decide about the choice of formulation, starting dose, the route of administration of MHT, and how to tailor MHT to each woman's individual situation, risks, and treatment goals. (Ungraded best practice statement)

Custom-compounded hormones

3.1i We recommend using MHT preparations approved by the US Food and Drug Administration (FDA) and comparable regulating bodies outside the United States and recommend against the use of custom-compounded hormones. (Ungraded best practice statement)

3.2 Conjugated equine estrogens with bazedoxifene

3.2 For symptomatic postmenopausal women with a uterus and without contraindications, we suggest the combination of conjugated equine estrogens (CEE)/bazedoxifene (BZA) (where available) as an option for relief of VMS and prevention of bone loss. (2|⊕⊕⊕○)

3.3 Tibolone

3.3a For women with bothersome VMS and climacteric symptoms and without contraindications, we suggest tibolone (in countries where available) as an alternative to MHT. (2|⊕⊕○○)

3.3b We recommend against adding tibolone to other forms of MHT. (1|⊕⊕○○)

3.3c We recommend against using tibolone in women with a history of breast cancer. (1|⊕⊕○○)

3.4 Clinical management of patients taking hormone therapies

Monitoring during therapy

3.4a For women with persistent unscheduled bleeding while taking MHT, we recommend evaluation to rule out pelvic pathology, most importantly, endometrial hyperplasia and cancer. (1|⊕⊕⊕○)

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing EPT and emphasizing the importance of adhering to age-appropriate breast cancer screening. (1|⊕⊕⊕○)

3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. (Ungraded best practice statement)

3.4d For young women with primary ovarian insufficiency (POI), premature or early menopause, without contraindications, we suggest taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. (2|⊕⊕○○)

Stopping considerations

3.4e For women preparing to discontinue MHT, we suggest a shared decision-making approach to elicit individual preference about adopting a gradual taper vs abrupt discontinuation. (2|⊕⊕○○)

The **American Congress of Obstetricians and Gynecologists (ACOG)'s** Clinical Guidelines on Management of Menopausal Symptoms recommended the following in 2014:

• Vasomotor symptoms are best managed with systemic HT, although alternatives such as SSRIs, SNRIs, and clonidine have been shown to be effective.

• Vaginal symptoms are best treated with systemic or topical HT, but topical methods are preferable as they have fewer adverse effects.

• Systemic HT should be given in the lowest dose and for the shortest period possible to decrease the risk of serious adverse events, such as thromboembolic disease and breast cancer.

Table 1. Treatment Options for Menopausal Symptoms

Brand	*Generic*	*Route*	*Effective dosage*	*Approved for vasomotor symptoms?*	*Approved for vaginal symptoms?*
Climara	Estradiol	Transdermal	0.025 mg per day	Yes	Yes
Duavee	Conjugated estrogen/bazedoxifene	Oral	0.45 mg/20 mg per day	Yes	No
Estrace	Micronized estradiol-17β	Oral	0.5 to 1.0 mg per day	Yes	Yes
Estrace cream	Micronized estradiol-17β	Topical	2 g per day	No	Yes
Estring	Estradiol-17β ring	Vaginal ring	2 mg per 90-day ring	No	Yes
Femring	Estradiol acetate	Vaginal ring	0.05 mg per day	No	Yes
Osphena	Ospemifene	Oral	60 mg per day	No	Yes
Paxil	Paroxetine	Oral	7.5 mg per day	Yes	No
Premarin	Conjugated estrogen	Oral	0.3 to 0.625 mg per day	Yes	Yes
Premarin vaginal	Conjugated estrogen	Topical	0.5 to 2 g per day	No	Yes
Vagifem	Estradiol	Vaginal tablet	10 mcg per day	No	Yes

NOTE: *The American College of Obstetricians and Gynecologists guidelines mention other treatment options. Only those approved for this indication by the U.S. Food and Drug Administration are listed in this table.*

The **Society of Obstetricians and Gynecologists of Canada in 2014** provided the following recommendation:

1. Health care providers should periodically review the risks and benefits of prescribing hormone therapy to a menopausal woman in light of the association between duration of use and breast cancer risk. (I-A)
2. Health care providers may prescribe hormone therapy for menopausal symptoms in women at increased risk of breast cancer with appropriate counselling and surveillance. (I-A)
3. Health care providers should clearly discuss the uncertainty of risks associated with systemic hormone therapy after a diagnosis of breast cancer in women seeking treatment for distressing symptoms (vasomotor symptoms or vulvovaginal atrophy). (I-B)

Guideline Ratings

Guideline Issuer and Date	NAMS 2017	AACE/ACE 2017	AFP 2016	NICE 2015	EC 2015	ACOG 2014	SOGC 2014
1. Transparency	B	B	C	A	A	B	B
2. Conflict of interest	A	NR	NR	A	A	NR	NR
3. Development group	A	B	C	A	A	B	NR
4. Systematic Review	B	B	B	A	A	B	B
5. Supporting evidence	B	B	A	A	A	B	A
6. Recommendations	B	B	A	B	A	B	B
7. External Review	NR	NR	NR	NR	NR	NR	NR
8. Currency and updates	B	B	B	B	B	B	B

See appendix B for full description of the Trustworthy Guideline grading system.

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Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations
Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything,

this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.
Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.