National Institute for Health and Care Excellence

Draft for consultation

Menopause (update)

[B1] Managing genitourinary symptoms (network meta-analyses)

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.4.19 to 1.4.25, 1.4.31 to 1.4.33 and 1.5.2 as well as research recommendations 3 and 5 in the NICE guideline

November 2023

Draft for consultation

These evidence reviews were developed by NICE

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Treatments for managing genitourinary symptoms associated with the menopause - network meta-analyses

Review question

What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Introduction

Genitourinary symptoms associated with the menopause include vaginal dryness, pain with sex (dyspareunia), vulvovaginal discomfort or irritation and discomfort or pain when urinating (dysuria), which are related to decreasing oestrogen levels in the menopause. These genitourinary symptoms may have a negative impact on the quality of life, requiring treatment with an appropriate and effective therapy.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women with troublesome genitourinary symptoms associated with the menopause.

Intervention	Interventions will be categorised into classes (each main bullet represents one class):
	• Vaginal oestrogens
	  ○ Estriol cream
	  ○ Estriol pessary (doses 30, 40, 50, 100 micrograms)
	  ○ Estriol gel
	  ○ Estradiol vaginal tablet/pessary
	  ○ Estradiol ring
	  ○ Estradiol gel
	  ○ Estradiol soft-gel capsule
	• Selective oestrogen receptor modulators
	  ○ Ospemifene
	• Dehydroepiandrosterone
	  ○ Prasterone pessary
	• Transvaginal laser therapy
	  ○ CO2 laser
	  ○ Erbium laser
	• Non hormonal local treatments
	  ○ Moisturisers and lubricants

Comparison	• Other active treatment
	• Placebo or sham treatment
	  ○ Topical creams and gels
	  ○ Tablets / pessaries
	  ○ Sham laser

	○ Ring • No treatment
Outcome	Critical • pain with sex (dyspareunia) • vulvovaginal dryness • vulvovaginal discomfort or irritation • discomfort or pain when urinating (dysuria) • discontinuation of treatment due to side effects Important • change in most bothersome symptom • distress, bother or interference of genitourinary symptoms • satisfaction with treatment *Note, if network meta-analysis is possible it will be done for critical outcomes only and separate pair-wise meta-analyses will not be done for important outcomes.*

CO2: carbon-dioxide
1. For network meta-analysis (NMA): Active interventions that are not part of the decision problem were included if they acted as connectors of the interventions of interest in the network.

For further details see the review protocol in Appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document (see Supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

After identification of the evidence the assessment of outcomes and interventions showed that a network meta-analysis (NMA) was possible for all critical outcomes apart from discomfort or pain when urinating for which pairwise analysis was carried out. As per protocol pairwise meta-analyses of other outcomes were therefore not conducted.

Overview of method of synthesis

Network meta-analysis is a generalisation of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials (see Appendix L for details). A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A versus B trial, is the same with the relative effect between A and B estimated indirectly from A versus C and B versus C trials. NMA techniques include both direct and indirect comparisons across treatments and allow simultaneous inference on the relative effect of all treatments that participate in a single 'network of evidence', where every treatment is linked to at least one of the other treatments under assessment through direct or indirect comparisons.

Included studies

39 studies reported in 40 publications were included for this review, which were all randomised controlled trials (RCTs: Archer 2015, Archer 2018, Archer 2019, Ayton 1996, Bachmann 1997, Bachmann 2008, Bachmann 2009, Bachmann 2010, Barentsen 1997,

Barton 2018, Bosak 2019, Bouchard 2015, Bumphenkiatikul 2020, Cagnacci 2022, Cano 2012, Chen 2013, Chompootaweep 1998, Constantine 2017, Cruz 2018, Dugal 2000, Eriksen 1992, Fernandes 2014, Garcia de Arriba 2022, Griesser 2012, Henriksson 1994, Hirschberg 2020, Labrie 2009, Labrie 2016, Li 2021, Lima 2013, Manonai 2001, Mitchell 2018, Pickar 2016, Poordast 2021, Portman 2013, Portman 2014, Ruanphoo 2020,Salvatore 2021, Tanmahasamut 2020, Weisberg 2005). One trial (Portman 2014) was reported in two publications, dividing patients according to their most bothersome symptom: pain with sex (Portman 2013) or vaginal dryness (Portman 2014).

The RCTs were all conducted in women with genitourinary symptoms associated with the menopause.

According to the treatments assessed and the types of outcomes reported in each RCT, the included RCTs have contributed data to one or more networks of evidence and respective NMAs.

For the outcome of vulvovaginal dryness, the network of evidence (and the respective NMA) included 25 RCTs (Archer 2015, Archer 2018, Archer 2019, Bachmann 2009, Bachmann 2010, Bouchard 2015, Bumphenkiatikul 2020, Cagnacci 2022, Chen 2013, Chompootaweep 1998, Constantine 2017, Cruz 2018, Dugal 2000, Eriksen 1992, Fernandes 2014, Hirschberg 2020, Labrie 2009, Labrie 2016, Li 2021, Mitchell 2018, Pickar 2016, Poordast 2021, Portman 2014 (dryness MBS subgroup), Salvatore 2021, Tanmahasamut 2020) comparing 17 interventions in 10 treatment classes with 4950 participants. For details of the interventions and comparisons included in this analysis see .

Table 3, Table 4, and Figure 2.

For the outcome of pain with sex (dyspareunia), the network of evidence (and the respective NMA) included 24 RCTs (Archer 2015, Archer 2018, Archer 2019, Bachmann 2009, Bachmann 2010, Bouchard 2015, Bumphenkiatikul 2020, Cagnacci 2022, Chompootaweep 1998, Constantine 2017, Cruz 2018, Eriksen 1992, Fernandes 2014, Garcia de Arriba 2022, Hirschberg 2020, Labrie 2009, Labrie 2016, Li 2021, Mitchell 2018, Pickar 2016, Poordast 2021, Portman 2014 (dyspareunia MBS subgroup), Salvatore 2021, Tanmahasamut 2020) comparing 16 interventions in 10 treatment classes with 5509 participants. For details of the interventions and comparisons included in this analysis see Table 5, Table 6, and Figure 2.

For the outcome of vulvovaginal discomfort/irritation, the network of evidence (and the respective NMA) included 13 RCTs (Archer 2018, Archer 2019, Bachmann 2008, Bachmann 2009, Bouchard 2015, Cagnacci 2022, Constantine 2017, Cruz 2018, Eriksen 1992, Hirschberg 2020, Li 2021, Poordast 2021, Salvatore 2021) comparing 13 interventions in 9 treatment classes with 3060 participants. For details of the interventions and comparisons included in this analysis see Table 7, Table 8, and Figure 3.

For the outcome of pain/discomfort when urinating (dysuria), the evidence included 3 RCTs (Li 2021, Poordast 2021, Salvatore 2021) comparing 4 interventions in 4 treatment classes with 211 participants. For details of the interventions and comparisons included in this analysis see Table 9 and Figure 4. **Outcome: Pain/discomfort when urinating (dysuria)**

The evidence for this outcome could not form a network as there was insufficient data to connect the classes. Therefore, a pairwise comparison was made, which showed no difference on pain/discomfort when urinating for the intervention lubricant versus conjugated oestrogen cream. There was some evidence suggesting a reduction in pain/discomfort when urinating for CO2 laser when compared to placebo, however the sample sizes in all included studies for this outcome were small, leading to uncertainty in the results (see Table 9).

Table 9For the outcome of discontinuation due to adverse events, the network of evidence (and the respective NMA) included 31 RCTs (Archer 2015, Archer 2018, Archer 2019, Ayton 1996, Bachmann 1997, Bachmann 2008, Bachmann 2009, Bachmann 2010, Barentsen 1997, Barton 2018, Bosak 2019, Bouchard 2015, Bumphenkiatikul 2020, Cano 2012, Chen 2013, Constantine 2017, Cruz 2018, Eriksen 1992, Fernandes 2014, Garcia de Arriba 2022, Griesser 2012, Henriksson 1994, Hirschberg 2020, Labrie 2016, Lima 2013, Li 2021, Manonai 2001, Pickar 2016, Poordast 2021, Portman 2014 (dryness MBS subgroup), Portman 2014 (dyspareunia MBS subgroup), Ruanphoo 2020) comparing 16 interventions in 8 treatment classes with 7503 participants. For details of the interventions and comparisons included in this analysis see Table 10, Table 11, and Figure 5.

The included studies are summarised in Table 2. See the literature search strategy in Appendix B and study selection flow chart in Appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Interventions	Outcomes
Archer 2015 RCT US/Canada	N=255 Arm 1 age, mean (SD) years: 59.37 (NR) Arm 2 age, mean (SD) years: 57.51 (NR) Arm 3 age, mean (SD) years: 58.81 (NR) Moderate to severe pain at sexual activity (at screening and on day 1) Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Low dose prasterone 0.25% (3.25mg) DHEA suppository- daily administration Arm 2: Prasterone 0.50% (6.5mg) DHEA suppository- daily administration Arm 3: Placebo Placebo pessary Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events
Archer 2018 RCT United States	N=576 Arm 1 age, mean (SD) years: 59.5 (6.7) Arm 2 age, mean (SD) years: 59.8 (6.1) Moderate to severe vaginal dryness (as most bothersome GU symptom) Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR	Arm 1: Oestradiol oestradiol vaginal cream 0.003% (0.5 g of cream daily for 2 weeks then 2 times per week) Arm 2: Placebo 0.5g placebo cream Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discomfort or pain when urinating (dysuria) • discontinuation due to adverse events
Archer 2019 RCT United States	N=627 Arm 1 age, mean (SD) years: 59.7 (6.6) Arm 2 age, mean (SD) years: 59.8 (7.2) Moderate to severe vaginal dryness (as most bothersome GU symptom) Uterus or not: Both uterus & no uterus	Arm 1: Ospemifene Ospemifene 60mg oral tablet; 1 per day for 12 weeks Arm 2: Placebo placebo oral tablet Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to adverse events

Study	Population	Interventions	Outcomes
	Breast or gynae cancer history: NR		
Ayton 1996 RCT Australia	N=194 Arm 1 age, mean (SD) years: 59.3 (7.3) Arm 2 age, mean (SD) years: 59.9 (7.3) Any symptoms of vaginal dryness with or without dyspareunia pruritus, dysuria and/or urgency, and signs of atrophic vaginitis. Uterus or not: Uterus Breast or gynae cancer history: None	Arm 1: Oestradiol Low dose estradiol vaginal ring (Estring) Arm 2: Conjugated oestrogen Conjugated equine oestrogen vaginal cream (Premarin). 1 g of cream (0.625 mg equine estrogens) every night for three weeks followed by one week free of treatment. Then cycle repeated. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• discontinuation due to adverse events
Bachmann 1997 RCT United States	N=196 Arm 1 age, mean (SD) years: 56.6 (NR) Arm 2 age, mean (SD) years: 57.3 (NR) Symptoms of vaginal dryness and one or more signs of vaginal atrophy Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR	Arm 1: Oestradiol Low dose oestradiol vaginal ring (Estring) Arm 2: Conjugated oestrogen Conjugated equine oestrogen vaginal cream (Premarin). 2 g of cream (1.250 mg equine oestrogens) 3 times per week. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• discontinuation due to adverse events
Bachmann 2008 RCT United States	N=230 Arm 1 age, mean (SD) years: 57.7 (6.5) Arm 2 age, mean (SD) years: 58.3 (7.4) Arm 3 age, mean (SD) years: 57.6 (4.8) Moderate to severe vaginal dryness and soreness. Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Oestradiol 10µg oestradiol vaginal tablet. Once daily for 2 weeks then twice-weekly for 10 weeks. Arm 2: Oestradiol 25µg oestradiol vaginal tablet. Once daily for 2 weeks then twice-weekly for 10 weeks. Arm 3: Placebo Placebo vaginal tablet. Once daily for 2 weeks then twice-weekly for 10 weeks. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal discomfort/irritation • discontinuation due to adverse events
Bachmann 2009 RCT US/Canada	N=423 Arm 1 age, mean (SD) years: 57.7 (5.8) Arm 2 age, mean (SD) years: 57.5 (5.5) Arm 3 age, mean (SD) years: 58 (5.8) Arm 4 age, mean (SD) years: 58.7 (5.8) Moderate to severe vaginal dryness, itching, and burning or dyspareunia. Uterus or not: Uterus Breast or gynae cancer history: NR	Arm 1: Conjugated oestrogen Conjugated equine oestrogen vaginal cream (Premarin). 0.5 g of cream (0.3 mg equine estrogens) every night for three weeks followed by one week free of treatment. Then cycle repeated. Arm 2: Conjugated oestrogen Conjugated equine oestrogen vaginal cream (Premarin). 0.5 g of cream (0.3 mg equine estrogens) twice weekly. Arm 3: Placebo Placebo vaginal cream. 0.5 g of cream every night for three weeks followed by one week free of treatment. Then cycle repeated. Arm 4: Placebo Placebo vaginal cream 0.5 g of cream twice weekly. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to adverse events
Bachmann 2010 RCT United States	N=826 Arm 1 age, mean (SD) years: 58.6 (6.3) Arm 2 age, mean (SD) years: 58.4 (6.3) Arm 3 age, mean (SD) years:	Arm 1: Ospemifene 60mg Ospemifene oral tablet daily. Arm 2: Low dose ospemifene 30mg Ospemifene oral tablet daily. Arm 3: Placebo Placebo oral tablet daily.	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events

Study	Population	Interventions	Outcomes
	58.9 (6.1) Moderate to severe vulvovaginal atrophy Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes, in all treatment arms	
Barentsen 1997 RCT Netherlands	N=165 Arm 1 age, mean (SD) years: 57.9 (NR) Arm 2 age, mean (SD) years: 58.5 (NR) Any signs or symptoms of vaginal atrophy Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR	Arm 1: Oestradiol Estradiol vaginal ring (Estring) with a constant release of around 7.5 µg estradiol/24 h for 90 days. Arm 2: Oestriol Vaginal oestriol cream (Synapause). 1 mg estriol/g of cream. 0.5 mg daily for the first 2 weeks then 0.5 mg three times weekly. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• discontinuation due to adverse events
Barton 2018 RCT United States	N=443 Arm 1 age, mean (SD) years: 56.8 (6.7) Arm 2 age, mean (SD) years: 57.3 (8.2) Arm 3 age, mean (SD) years: 58 (7.3) Moderate to severe vaginal dryness or dyspareunia Uterus or not: Both uterus & no uterus Breast or gynae cancer history: Breast or gynae cancer	Arm 1: Low dose prasterone 0.25% (3.25mg) DHEA in moisturiser gel - via syringe applicator. Daily for 12 weeks Arm 2: Prasterone 0.50% (6.5mg) DHEA in moisturiser gel - via syringe applicator. Daily for 12 weeks Arm 3: Moisturiser Moisturiser gel- via syringe applicator. Daily for 12 weeks Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes, in all treatment arms	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events
Bosak 2019 RCT Iran, Islamic Republic of	N=64 Arm 1 age, mean (SD) years: 53.8 (3.2) Arm 2 age, mean (SD) years: 53.7 (2) Vaginal atrophy symptoms and dyspareunia Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Conjugated oestrogen Conjugated estrogen cream (daily for 2 weeks then 2 times per week for the next 10 weeks) Arm 2: Placebo Placebo gel (daily for 2 weeks then 2 times per week for the next 10 weeks) Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No	• pain with sex (dyspareunia) • discontinuation due to adverse events
Bouchard 2015 RCT US/Canada	N=450 Arm 1 age, mean (SD) years: 58.33 (NR) Arm 2 age, mean (SD) years: 58.41 (NR) Arm 3 age, mean (SD) years: 57.59 (NR) Moderate to severe vaginal dryness as the most bothersome vaginal atrophy symptom Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Prasterone 0.50% (6.5mg) DHEA suppository- daily administration for 2 weeks, then 2x/week for 10 weeks Arm 2: Low dose prasterone 0.25% (3.25mg) DHEA suppository- daily administration for 2 weeks, then 2x/week for 10 weeks Arm 3: Placebo Placebo pessary- daily administration for 2 weeks, then 2x/week for 10 weeks Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to adverse events
Bumphenkiatikul 2020 RCT Thailand	N=67 Arm 1 age, mean (SD) years: 57.41 (4.85) Arm 2 age, mean (SD) years: 57.03 (4.65)	Arm 1: Conjugated oestrogen Conjugated estrogen 0.625mg vaginal tablet (daily for 3 weeks then 2 times per week for the next 9 weeks) Arm 2: Placebo Placebo vaginal tablet (daily for 3 weeks then 2 times per week for the next 9	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to

Study	Population	Interventions	Outcomes
	Moderate to severe vaginal atrophy symptoms Uterus or not: NR Breast or gynae cancer history: None	weeks) Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	adverse events
Cagnacci 2022 RCT Romania	N=56 Arm 1 age, mean (SD) years: 48.76 (3.18) Arm 2 age, mean (SD) years: 50.23 (2.52) Vulvovaginal atrophy Uterus or not: NR Breast or gynae cancer history: None	Arm 1: Moisturiser Intravaginal polycarbophil moisturizer gel. 1 g of PCV gel (Ainara) twice a week for 30 days. Arm 2: Lubricant Intravaginal hyaluronic acid gel .3 g of gel (Hyalo Gyn) 3 times per week for 30 days. Treatment duration (weeks): 4.3 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to adverse events
Cano 2012 RCT Spain	N=167 Arm 1 age, mean (SD) years: 56.5 (5.72) Arm 2 age, mean (SD) years: 57.2 (6.7) Symptoms of vaginal dryness Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Oestriol Estriol gel, 50ug Arm 2: Placebo Placebo gel Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• discontinuation due to adverse events
Chen 2013 RCT China	N=144 Arm 1 age, mean (SD) years: 54.05 (4.27) Arm 2 age, mean (SD) years: 54.41 (4.6) Symptoms of vaginal dryness Uterus or not: NR Breast or gynae cancer history: None	Arm 1: Lubricant Hyaluronic acid vaginal gel (Hyalofemme). 0.5g once every 3 days for 30 days Arm 2: Oestriol 0.5g Estriol cream. 0.5g once every 3 days for 30 days Treatment duration (weeks): 4.29 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol	• vulvovaginal dryness • discontinuation due to adverse events
Chompoota weep 1998 RCT Thailand	N=40 Arm 1 age, mean (SD) years: 54.2 (4.9) Arm 2 age, mean (SD) years: 54.7 (4) Urogenital symptoms (defined as vaginal dryness, burning, itching, dyspareunia, dysuria, etc) Uterus or not: NR Breast or gynae cancer history: None	Arm 1: Oestradiol 250ug levonorgestrel + 30ug ethinyl oestradiol tablet - take intravaginally. Arm 2: Oestradiol 0.625mg oestradiol cream Treatment duration (weeks): 8 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events
Constantine 2017 RCT US/Canada	N=375 Arm 1 age, mean (SD) years: 58.6 (6.3) Arm 2 age, mean (SD) years: 59.4 (6) Moderate to severe dyspareunia Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Oestradiol f TX-004HR vaginal oestradiol (10µg) soft-gel capsules Arm 2: Placebo Placebo vaginal capsule Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to adverse events
Cruz 2018 RCT Brazil	N=45 Arm 1 age, mean (SD) years: 55.9 (5.2) Arm 2 age, mean (SD) years: 56.9 (6) Arm 3 age, mean (SD) years:	Arm 1: CO2 laser CO2 vaginal laser (SmartXide2 system, MonaLisa Touch) + placebo vaginal cream Arm 2: Oestriol sham laser treatment (same intravaginal & vulvar probes but no pulse delivered) + vaginal estriol cream	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to

Study	Population	Interventions	Outcomes
	55.7 (4.4) One moderate symptom of VVA Uterus or not: NR Breast or gynae cancer history: None	Arm 3: CO2 laser + oestriol CO2 vaginal laser (SmartXide2 system, MonaLisa Touch) + estriol cream 3x/week for 20 weeks Treatment duration (weeks): 20 Lubricant/moisturizer permitted: No	adverse events
Dugal 2000 RCT Norway	N=96 Arm 1 age, mean (SD) years: 58.2 (4.9) Arm 2 age, mean (SD) years: 59.3 (5.3) Symptoms of vaginal atrophy Uterus or not: NR Breast or gynae cancer history: None	Arm 1: Oestradiol Estradiol vaginal tablets, 25ug, , daily for 2 weeks then 2 tablets weekly Arm 2: Oestriol Estriol suppositories, 0.5mg, , daily for 2 weeks then 2 pessaries weekly Treatment duration (weeks): 24 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • discontinuation due to adverse events
Eriksen 1992 RCT Denmark	N=154 Arm 1 age, mean (SD) years: 58.1 (6) Arm 2 age, mean (SD) years: 58.6 (6) Symptoms of vaginal atrophy Uterus or not: NR Breast or gynae cancer history: None	Arm 1: Oestradiol Estradiol vaginal tablets, 25ug (Vagifem) Arm 2: Placebo Placebo tablets Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to adverse events
Fernandes 2014 RCT Brazil	N=80 Arm 1 age, mean (SD) years: 57 (5.4) Arm 2 age, mean (SD) years: 56.2 (5.3) Arm 3 age, mean (SD) years: 56.4 (4.8) Arm 4 age, mean (SD) years: 57.7 (4.7) Symptoms of vaginal atrophy Uterus or not: Uterus Breast or gynae cancer history: None	Arm 1: Moisturiser polyacrylic acid vaginal cream (Vagidrat) Arm 2: Testosterone testosterone vaginal cream, 300ug Arm 3: Conjugated oestrogen conjugated estrogen 0.625mg vaginal cream Arm 4: Lubricant glycerin gel Treatment duration (weeks): 12 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events
Garcia de Arriba 2022 RCT Germany/Switzerland	N=172 Arm 1 age, mean (SD) years: 61.7 (6.9) Arm 2 age, mean (SD) years: 59.5 (7.3) Vulvovaginal dryness moderate or severe Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR	Arm 1: Oestriol Ovestin estriol cream 1mg estriol in 1g cream - once daily for first 3 weeks then twice weeky Arm 2: Moisturiser Vagisan moisturizing cream intravaginally once per day, outer genital area several times per day as needed Treatment duration (weeks): 6.14 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events
Griesser 2012 RCT Germany	N=436 Arm 1 age, mean (SD) years: 64.9 (8.1) Arm 2 age, mean (SD) years: 65.4 (7.3) Arm 3 age, mean (SD) years: 64.8 (7.8) Symptoms of vaginal atrophy Uterus or not: NR Breast or gynae cancer history: None	Arm 1: Oestriol estriol pessary, 0.2mg, once daily application for 20 days, then 2x/week Arm 2: Oestriol estriol pessary, 0.03mg, once daily application for 20 days, then 2x/week Arm 3: Placebo Placebo pessary, once daily application for 20 days, then 2x/week Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • discontinuation due to adverse events
Henriksson 1994 RCT	N=165 Arm 1 age, mean (SD) years:	Arm 1: Oestradiol oestradiol vaginal ring, 2mg Arm 2: Oestriol	• discontinuation due to adverse events

Study	Population	Interventions	Outcomes
Sweden/Finland/Denmark	59.2 (6.5) Arm 2 age, mean (SD) years: 59.8 (7.2) Symptoms of vaginal atrophy Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	estriol pessary, 0.5mg, once daily application for first 3 weeks, then 2x/week Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	
Hirschberg 2020 RCT Spain	N=61 Arm 1 age, mean (SD) years: 58.9 (7.6) Arm 2 age, mean (SD) years: 61.4 (4.7) Moderate to severe vaginal dryness Uterus or not: Both uterus & no uterus Breast or gynae cancer history: Breast cancer	Arm 1: Oestriol 0.005% estriol vaginal gel Arm 2: Moisturiser moisturizing gel. 1 g of gel per application for 12 weeks: once daily during the first three weeks, and then twice weekly Treatment duration (weeks): 12 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discontinuation due to adverse events
Labrie 2009 RCT Canada	N=216 Arm 1 age, mean (SD) years: NR(NR) Arm 2 age, mean (SD) years: NR(NR) Arm 3 age, mean (SD) years: NR(NR) Arm 4 age, mean (SD) years: NR(NR) Moderate or severe vaginal dryness/irritation/dyspareunia Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Low dose prasterone Prasterone ovule, 3.25mg Arm 2: Prasterone Prasterone ovule, 6.5mg Arm 3: High dose prasterone Prasterone ovule, 13mg Arm 4: Placebo Placebo Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia)
Labrie 2016 RCT Canada	N=482 Arm 1 age, mean (SD) years: 59.5 (NR) Arm 2 age, mean (SD) years: 59.6 (NR) Moderate to severe pain with sex Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Prasterone Prasterone ovule, 6.5mg Arm 2: Placebo Placebo Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events
Li 2021 RCT Australia	N=85 Arm 1 age, mean (SD) years: 55 (7) Arm 2 age, mean (SD) years: 58 (8) Dyspareunia, burning, itching, or dryness severe enough to need treatment Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR	Arm 1: CO2 laser fractional microablative co2 laser (SmartXide2V2LR, MonaLisa Touch, DEKA Laser) Arm 2: Placebo Sham laser treatment done at minimal energy settings - with no tissue effects. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discomfort or pain when urinating (dysuria) • discontinuation due to adverse events
Lima 2013 RCT Brazil	N=90 Arm 1 age, mean (SD) years: 57 (NR) Arm 2 age, mean (SD) years: 56 (NR) Arm 3 age, mean (SD) years: 57 (NR)	Arm 1: Phyto cream Isoflavone vaginal gel 4%, 1g, once daily. Arm 2: Conjugated oestrogen CEE vaginal cream, 0.5g, once daily. Arm 3: Placebo Placebo cream, 1g, once daily. Treatment duration (weeks): 12	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events

Study	Population	Interventions	Outcomes
	Any vulvovaginal symptoms Uterus or not: Uterus Breast or gynae cancer history: None	Lubricant/moisturizer permitted: NR	
Manonai 2001 RCT Thailand	N=53 Arm 1 age, mean (SD) years: 55.1 (4.7) Arm 2 age, mean (SD) years: 55.8 (4.7) Any urogenital symptoms Uterus or not: NR Breast or gynae cancer history: None	Arm 1: Oestradiol Vaginal oestradiol tablet (25µg oestradiol), daily for 2 weeks then twice weekly for 10 weeks. Arm 2: Conjugated oestrogen CEE vaginal cream. 1g (0.625 mg CEE) daily for 2 weeks then twice weekly for 10 weeks. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events
Mitchell 2018 RCT United States	N=302 Arm 1 age, mean (SD) years: 61 (4) Arm 2 age, mean (SD) years: 61 (4) Arm 3 age, mean (SD) years: 61 (4) Moderate to severe vulvovaginal itching, pain, irritation, or dryness Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Oestradiol Vagifem 10-µg oestradiol tablet + placebo vaginal gel. Vaginal tablet daily for 2 weeks, then twice weekly for the remaining 10 weeks, and the vaginal moisturizer every 3 days. Arm 2: Moisturiser Placebo vaginal tablet + Replens vaginal moisturizer. Vaginal tablet daily for 2 weeks, then twice weekly for the remaining 10 weeks, and the vaginal moisturizer every 3 days. Arm 3: Placebo Placebo tablet + placebo gel Treatment duration (weeks): 12 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol	• vulvovaginal dryness • pain with sex (dyspareunia)
Pickar 2016 RCT United States	N=50 Arm 1 age, mean (SD) years: 62.4 (5.7) Arm 2 age, mean (SD) years: 62.6 (7.3) Moderate-to-severe vaginal dryness, vaginal pain associated with sexual activity, vaginal and/or vulvar irritation/itching, dysuria, or vaginal bleeding associated with sexual activity Uterus or not: NR Breast or gynae cancer history: NR	Arm 1: Oestradiol 10mg TX-004HR vaginal E2 softgel vaginal capsules (TherapeuticsMD) intravaginally once-daily for 14 days Arm 2: Placebo placebo softgel vaginal capsules intravaginally once-daily for 14 days Treatment duration (weeks): 2 Lubricant/moisturizer permitted: NR	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discomfort or pain when urinating (dysuria) • discontinuation due to adverse events
Poordast 2021 RCT Iran, Islamic Republic of	N=66 Arm 1 age, mean (SD) years: 61.2 (10.28) Arm 2 age, mean (SD) years: 59.6 (8.29) Urogenital symptoms Uterus or not: Uterus Breast or gynae cancer history: None	Arm 1: Conjugated oestrogen CEE vaginal cream. 5mg daily (0.62mg CEE per 1g cream) for 2 weeks then 3 times per week for 4 weeks. Arm 2: Lubricant Aloe vera vaginal gel (2% Aloe vera powder). 5mg daily for 2 weeks then 3 times per week for 4 weeks. Treatment duration (weeks): 6 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discomfort or pain when urinating (dysuria) • discontinuation due to adverse events
Portman 2013 (dyspareunia MBS subgroup) RCT United States	N=605 Arm 1 age, mean (SD) years: 58 (6.4) Arm 2 age, mean (SD) years: 58.1 (6) Moderate-to-severe dyspareunia as MBS Uterus or not: Both uterus & no uterus	Arm 1: Ospemifene ospemifene 60 mg oral tablet once daily Arm 2: Placebo placebo oral tablet once daily Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms	• pain with sex (dyspareunia) • discontinuation due to adverse events

Study	Population	Interventions	Outcomes
	Breast or gynae cancer history: None		
Portman 2014 (dryness MBS subgroup) RCT United States	N=314 Arm 1 age, mean (SD) years: 59.9 (6.7) Arm 2 age, mean (SD) years: 59.3 (7) Moderate-to-severe vaginal dryness as MBS Uterus or not: NR Breast or gynae cancer history: NR	Arm 1: Ospemifene ospemifene 60 mg oral tablet once daily Arm 2: Placebo placebo oral tablet once daily Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms	• vulvovaginal dryness • discontinuation due to adverse events
Ruanphoo 2020 RCT Thailand	N=88 Arm 1 age, mean (SD) years: 61.73 (8.01) Arm 2 age, mean (SD) years: 59.84 (7.49) Moderate to severe vaginal atrophy symptoms Uterus or not: NR Breast or gynae cancer history: NR	Arm 1: CO2 laser Fractional microablative CO2 laser (MonaLisa Touch, DEKA) treatment Arm 2: Placebo Sham laser treatment (same intravaginal & vulvar probes but no pulse delivered) Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No	• discontinuation due to adverse events
Salvatore 2021 RCT Italy/Greece	N=60 Arm 1 age, mean (SD) years: 57 (6.9) Arm 2 age, mean (SD) years: 58.4 (6) Genitourinal syndrome of menopause with vaginal dryness or dyspareunia as MBS Uterus or not: NR Breast or gynae cancer history: None	Arm 1: CO2 laser Microablative fractional CO2 laser (SmartXide2 V2LR, Monalisa Touch; DEKA) Arm 2: Placebo Sham fractional CO2 laser (SmartXide2 V2LR, Monalisa Touch; DEKA) - using non-ablative low dose (0.5W) Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort/irritation • discomfort or pain when urinating (dysuria) • discontinuation due to adverse events
Tanmahasamut 2020 RCT Thailand	N=80 Arm 1 age, mean (SD) years: 54.9 (9.79) Arm 2 age, mean (SD) years: 56.43 (4.47) Any post-menopausal vaginal symptoms Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None	Arm 1: Oestradiol Estradiol in KY-jelly lubricant gel. 2 mL (25µg estradiol) applied intravaginally daily for 2 weeks, and two doses per week for the next 6 weeks. Arm 2: Lubricant KY-jelly lubricant/ 2 mL applied intravaginally daily for 2 weeks, and two doses per week for the next 6 weeks. Treatment duration (weeks): 8 Lubricant/moisturizer permitted: Yes in all treatment arms	• vulvovaginal dryness • pain with sex (dyspareunia) • discontinuation due to adverse events
Weisberg 2005 RCT Australia	N=185 Arm 1 age, mean (SD) years: 58.1 (NR) Arm 2 age, mean (SD) years: 57.5 (NR) Significant signs or symptoms of urogenital atrophy Uterus or not: Uterus Breast or gynae cancer history: NR	Arm 1: Oestradiol Estring - vaginal ring containing 2mg micronized 17-beta-estradiol. Releases 8µg per 24hrs over 90 days. Arm 2: Oestradiol Vagifem - vaginal tablet 2µg micronized 17-beta-estradiol. Once daily for 2 weeks then twice per week. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR	• discontinuation due to adverse events

MBS: most bothersome symptom; NR: not reported; SD: standard deviation; VVA: vulvovaginal atrophy.

See the full evidence tables in Appendix D, the NMA forest plots in Appendix E and the NMA data extraction in Supplement 8.

Summary of the evidence

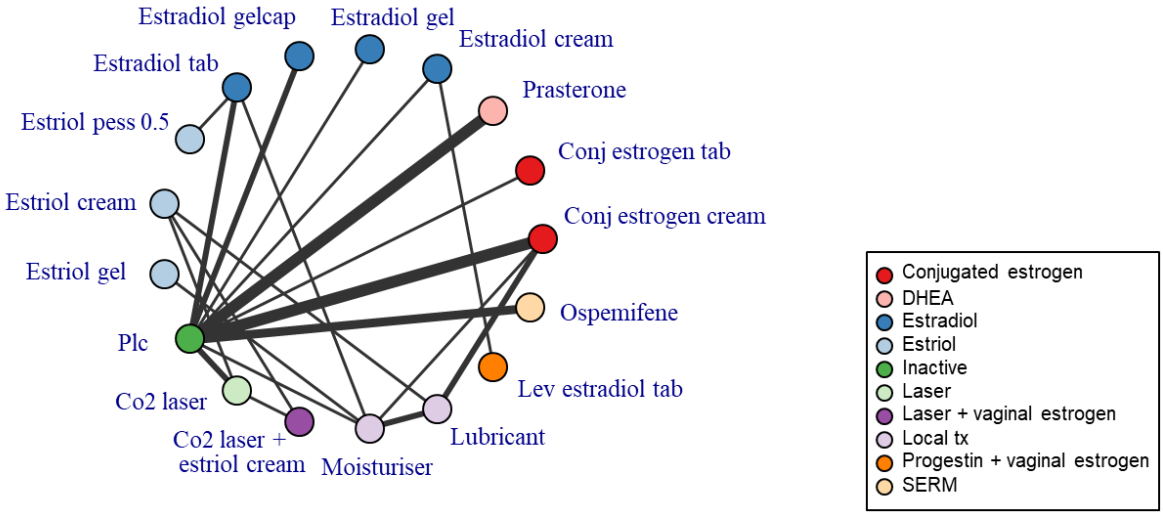
The network plots for each outcome are shown in Figure 1 to Figure 5. In each network plot, the width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of observations made on each treatment class (which is the sum of the number of participants). In addition, the numbers of observations on each treatment class, and on each intervention within class, are shown in Table 4, Table 6, Table 8, Table 9, and Table 11.

See the full evidence tables in Appendix D, the NMA forest plots in Appendix E and the NMA results including effects versus placebo and ranking tables in Appendix L. Where bias models suggested evidence of bias, bias-adjusted effects versus placebo and corresponding ranking tables are also shown. Full NMA methods including NMA models, inconsistency checks, bias-adjusted models, as well as NMA results are also provided in Appendix L.

Outcome: Vulvovaginal dryness (dryness)

Figure 1 shows the available interventions for all studies identified that reported this outcome.

Figure 1: Network diagram of all studies included in analysis by intervention. Vulvovaginal dryness.



Plc: placebo

The evidence suggested that the classes laser, laser + vaginal oestrogen, SERM, DHEA, conjugated oestrogen, and oestradiol (in order of effectiveness) showed decreased vulvovaginal dryness when compared to placebo. Estriol and progestin + vaginal oestrogen also showed some evidence of decreased dryness compared to placebo.

Table 3 shows laser + vaginal oestrogen and laser as the most effective intervention, however these results are based on small numbers of participants as shown in Table 6.

Table 3. Posterior median rank and 95% credible intervals by class. Vulvovaginal dryness.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Laser + vaginal oestrogen	1.59	1 (1, 5)
Laser	2.22	2 (1, 5)
Progestin + vaginal oestrogen	3.81	3 (1, 10)

Class	Posterior mean rank	Posterior median rank (95% CrI)
SERM	5.15	5 (2, 9)
DHEA	5.39	5 (2, 9)
Estriol	6.04	6 (3, 9)
Conjugated oestrogen	6.06	6 (3, 9)
Oestradiol	6.42	7 (4, 9)
Local treatments	8.78	9 (6, 10)
Inactive	9.54	10 (8, 10)

DHEA: dehydroepiandrosterone ; SERM: Selective estrogen receptor modulator

Table 4: Interventions, classes and number of patients (N) included in vulvovaginal dryness.

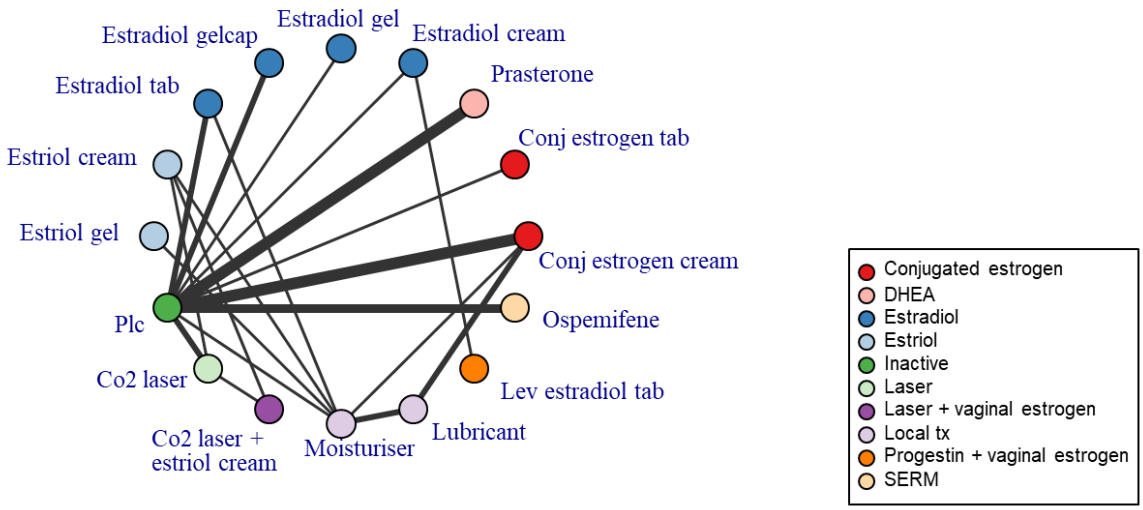
Intervention	N	Class	N
Placebo	2145	Inactive	2145
Prasterone	618	DHEA	618
CO2 laser	88	Laser	88
CO2 laser + oestriol cream	15	Laser + vaginal oestrogen	15
Moisturiser	160	Local treatment	312
Lubricant	152		
Levonorgestrel oestradiol tablet	20	Progestin + vaginal oestrogen	20
Ospemifene	749	SERM	749
Estriol cream	87	Estriol	185
Estriol pessary 50	48		
Estriol gel	50		
Oestradiol tablet	225	Oestradiol	784
Oestradiol gel	40		
Oestradiol cream	307		
Oestradiol soft-gel capsule	212		
Conjugated oestrogen tablet	34	Conjugated oestrogen	370
Conjugated oestrogen cream	336		

DHEA: dehydroepiandrosterone ; SERM: Selective estrogen receptor modulator

Outcome: Pain with sex (dyspareunia)

Figure 2 shows the available interventions for all studies identified that reported this outcome.

Figure 2: Network diagram of all studies included in analysis by intervention. Pain with sex.



Plc: placebo

The evidence suggested that the classes laser + vaginal oestrogen, laser, oestriol, conjugated oestrogen, DHEA, SERM, and oestradiol (in order of effectiveness) showed decreased pain with sex when compared to placebo.

Table 5 shows laser + vaginal oestrogen and laser as the most effective intervention, however these results are based on small numbers of participants as shown in Table 6.

Table 5. Posterior median rank and 95% credible intervals by class. Pain with sex.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Laser + vaginal oestrogen	1.56	1 (1, 6)
Laser	2.31	2 (1, 5)
Oestriol	4.53	4 (2, 9)
Conjugated oestrogen	4.67	4 (2, 8)
DHEA	4.96	5 (2, 9)
Progestin + vaginal oestrogen	6.30	7 (1, 10)
SERM	6.36	6 (3, 9)
Oestradiol	6.68	7 (3, 9)
Local treatments	8.06	8 (5, 10)
Inactive	9.57	10 (8, 10)

DHEA: dehydroepiandrosterone; SERM: Selective estrogen receptor modulator

Table 6: Interventions, classes and number of patients (N) included in pain with sex analysis.

Intervention	N	Class	N
Placebo	2293	Inactive	2293
Prasterone	618	DHEA	618
CO2 laser	88	Laser	88
CO2 laser + estriol cream	15	Laser + vaginal oestrogen	15
Moisturiser	247	Local treatment	327
Lubricant	80		
Levonorgestrel oestradiol tablet	20	Progestin + vaginal oestrogen	20

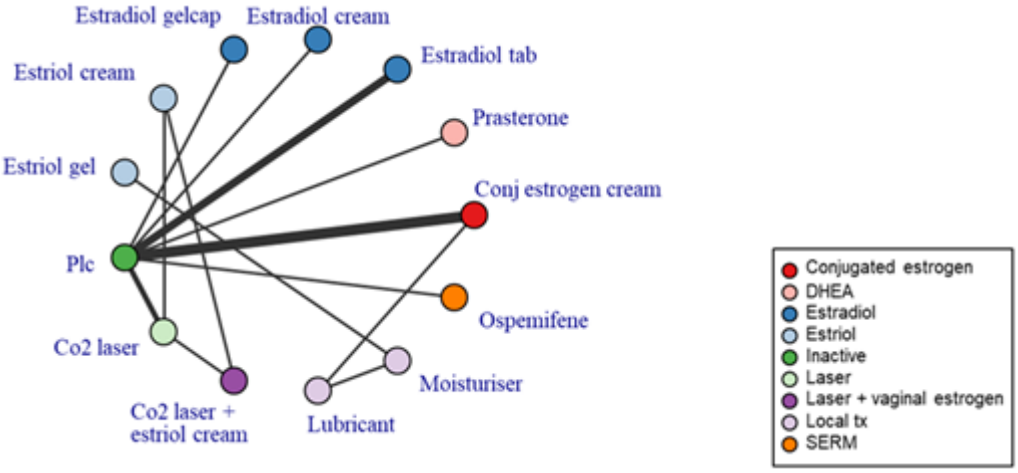
Intervention	N	Class	N
Ospemifene	892	SERM	892
Estriol cream	100	Estriol	150
Estriol gel	50		
Oestradiol tablet	177	Oestradiol	736
Oestradiol gel	40		
Oestradiol cream	307		
Oestradiol soft-gel capsule	212		
Conjugated oestrogen tablet	34	Conjugated oestrogen	370
Conjugated oestrogen cream	336		

DHEA: dehydroepiandrosterone; SERM: Selective estrogen receptor modulator

Outcome: Vulvovaginal discomfort/irritation (Discomfort)

Figure 3 shows the available interventions for all studies identified that reported this outcome.

Figure 3: Network diagram of all studies included in analysis by intervention. Vulvovaginal discomfort/irritation.



Plc: placebo

The evidence suggested that the classes laser and oestradiol (in order of effectiveness) showed decreased vulvovaginal discomfort/irritation when compared to placebo (Table 7). The evidence shows laser + vaginal oestrogen as the most effective treatment.

Table 7. Posterior median rank and 95% credible intervals by class. Vulvovaginal discomfort/irritation.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Laser + vaginal oestrogen	1.52	1 (1, 6)
Laser	2.64	2 (1, 6)
Oestradiol	3.75	4 (1, 7)
DHEA	3.82	3 (1, 9)
SERM	5.82	6 (2, 9)
Inactive	5.96	6 (4, 8)
Oestriol	6.56	7 (2, 9)
Conjugated oestrogen	7.04	7 (4, 9)

Class	Posterior mean rank	Posterior median rank (95% CrI)
Local treatment	7.87	8 (4, 9)

DHEA: dehydroepiandrosterone; SERM: Selective estrogen receptor modulator

Table 8: Interventions, classes and number of patients (N) included in vulvovaginal discomfort/irritation analysis.

Intervention	N	Class	N
Placebo	1280	Inactive	1280
Prasterone	150	DHEA	150
CO2 laser	88	Laser	88
CO2 laser + estriol cream	15	Laser + vaginal oestrogen	15
Moisturiser	40	Local treatment	100
Lubricant	60		
Ospemifene	313	SERM	313
Oestriol cream	15	Estriol	65
Oestriol gel	50		
Oestradiol tablet	258	Oestradiol	733
Oestradiol cream	287		
Oestradiol soft-gel capsule	188		
Conjugated oestrogen cream	316	Conjugated oestrogen	316

DHEA: dehydroepiandrosterone; SERM: Selective estrogen receptor modulator

Outcome: Pain/discomfort when urinating (dysuria)

The evidence for this outcome could not form a network as there was insufficient data to connect the classes. Therefore, a pairwise comparison was made, which showed no difference on pain/discomfort when urinating for the intervention lubricant versus conjugated oestrogen cream. There was some evidence suggesting a reduction in pain/discomfort when urinating for CO2 laser when compared to placebo, however the sample sizes in all included studies for this outcome were small, leading to uncertainty in the results (see Table 9).

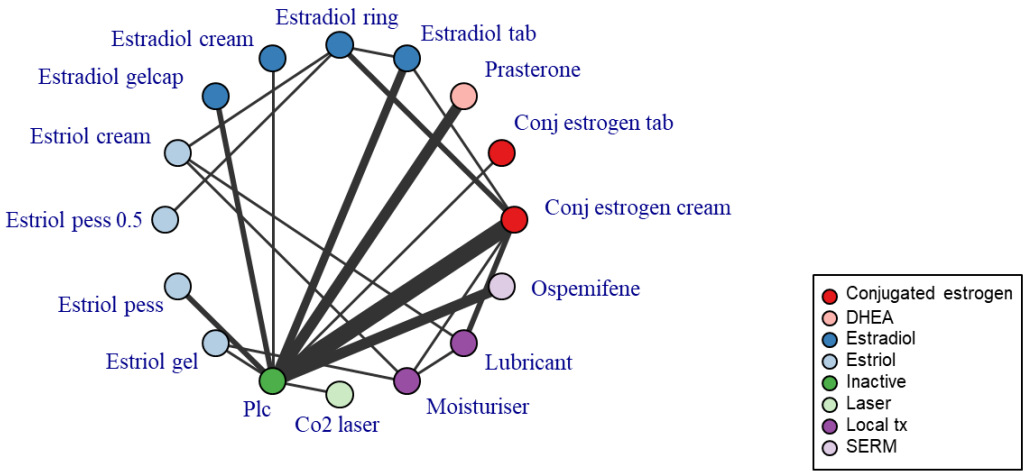
Table 9: Interventions, classes and number of patients (N) included in pain/discomfort when urinating analysis (dysuria).

Intervention	N	Class	N
Placebo	72	Inactive	72
CO2 laser	73	Laser	73
Lubricant	33	Local treatment	33
Conjugated oestrogen cream	33	Conjugated oestrogen	33

Outcome: Discontinuation due to adverse events

Figure 4 shows the available interventions for all studies identified that reported this outcome.

Figure 4: Network diagram of all studies included in analysis by intervention. Discontinuation due to adverse events.



Plc: placebo

The evidence suggested that local treatments (moisturiser and lubricant) compared to placebo showed the lowest odds of discontinuation due to adverse events (Table 10). There was some weaker, less clear evidence that showed increased odds of discontinuation due to adverse events for oestradiol compared to placebo, and conjugated oestrogen compared to placebo.

Table 10. Posterior mean and median rank and 95% credible intervals by class. Discontinuation due to adverse events.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Local treatments	1.15	1 (1, 3)
Inactive	3.24	3 (2, 5)
DHEA	4.19	4 (2, 8)
Oestriol	4.29	4 (2, 8)
SERM	4.36	4 (2, 7)
Oestradiol	5.82	6 (3, 8)
Conjugated oestrogen	6.38	7 (3, 8)
Laser	6.58	8 (1, 8)

DHEA: dehydroepiandrosterone; SERM: Selective estrogen receptor modulator

Table 11: Interventions, classes and number of patients (N) included in discontinuation due to adverse events analysis.

Intervention	N	Class	N
Placebo	2685	Inactive	2685
Prasterone	711	DHEA	711
CO2 laser	45	Laser	45
Moisturiser	120	Local treatment	247
Lubricant	127		
Ospemifene	1052	SERM	1052
Oestriol cream	239	Oestriol	747
Oestriol pessary	289		
Oestriol pessary 50	53		
Oestriol gel	166		
Oestradiol tablet	344	Oestradiol	1424
Oestradiol ring	581		
Oestradiol cream	287		

Intervention	N	Class	N
Oestradiol soft-gel capsule	212		
Conjugated oestrogen tablet	35	Conjugated oestrogen	592
Conjugated oestrogen cream	557		

DHEA: dehydroepiandrosterone; SERM: Selective estrogen receptor modulator

Quality assessment of studies included in the evidence review

NMA models that adjusted for small study bias were fitted. Bias-adjusted NMA models and results are shown in Appendix L.

Economic evidence

Included studies

One economic study was identified which was relevant to this question (Dymond 2021). The study compared ospemifene plus standard of care (SoC) to SoC alone in post-menopausal women with vaginal atrophy.

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in Supplement 2.

Summary of included economic evidence

See

Table 12 for the economic evidence profile of the included evidence.

Table 12: Economic evidence profile for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect (QALYs)	Cost effectiveness	
NICE 2023 1) Estriol 2) Estradiol 3) Prasterone 4) Ospemifene 5) Laser Vs Non-hormonal moisturiser and lubricant	Minor limitations	Directly applicable[1]	Bespoke economic model developed for this guideline	1)-£3 2)£12 3)£35 4)£360 5)£2,727	1)0.0171 2)0.0066 3)0.0139 4)0.0080 5)0.0320	Laser vs Estriol £183,260 per QALY gained. Estriol is both less expensive and more effective than all other treatments. Estriol is the preferred option at a £20,000 per QALY threshold.	Probability preferred option at £20k per QALY threshold Estriol 60.0% Prasterone: 31.4% Estradiol 7.0% All other interventions had a probability less than 1%
Dymond 2021 Ospemifene plus standard of care (SoC) vs SoC alone	Potentially serious limitations[2]	Directly applicable[1]	Model funded by manufacturer of ospemifene	£847	0.06	£14,138 per QALY gained	89% probability ospemifene is cost effective at a £20,000 per QALY threshold

[1] The models took a UK NHS perspective and utility values were valued using the EQ-5D questionnaire in the population covered by the model and scored using UK general population tariffs.

[2] Main effect estimates in the model were taken from a limited number of trials and may not represent the best evidence on effectiveness

Economic model

A bespoke economic model was developed for this topic that compared the cost utility of interventions for treating bothersome genitourinary symptoms associated with the menopause. The model compared estriol, estradiol, prasterone, ospemifene and laser to a comparator of non-hormonal moisturiser or lubricant. The full economic model is reported in Appendix I.

The economic model is a Markov model consisting of four states, none, mild and 'moderate or severe' symptoms based on the menopause rating scale. The hypothetical cohort were all assumed to be in the 'moderate or severe' state at the start of the model and would move between states over the first 12 weeks of the model based on effectiveness evidence around estimated in the accompanying NMAs of vulvovaginal dryness and dyspareunia. The model had a time horizon of 1 year with a sensitivity analysis extending that to 10 years. This was considered sufficiently long enough to all differences between interventions and that a majority of women would have either switched or discontinued treatment by the end of this period. As follow-up in the RCTs included in the accompanying NMA had limited follow-up a range of assumptions around continued treatment effect were considered.

Utility values for the health states in the model were taken from a survey of 1096 post-menopausal women between 40 and 75 years of age and stratified responses by the states reported in this economic model. Quality of life was assessed using the EQ-5D-3L questionnaire and converted into health utility scores using the UK general population value set. These values were highly applicable to the decision problem under consideration.

The cost of the interventions were taken from the BNF apart from laser which was estimated from a median of prices accessed online and from committee assumption. Appointment costs for gynaecologists and GPs were taken from NHS cost collection and PSSRU Unit Costs of Health and Social Care respectively.

In the base-case analysis, estriol was the preferred option when a threshold of £20,000 per QALY gained was used. Estriol remained the preferred option in all analyses apart from when favourable assumptions around the continuation of treatment effect and when the costs of interventions which could be purchased over the counter were removed where laser became the preferred option. For people who were not suitable or did not wish to take local vaginal oestrogen treatments, prasterone was the preferred option in the economic evaluation.

Probabilistic sensitivity analysis conformed the robustness of the results with estriol having a 60% probability of being the preferred option at £20,000 per QALY gained threshold. Laser, despite being the 'best performing' intervention in the accompanying NMA did not have a greater than 50% probability of being the preferred option until values for a willingness-to-pay per QALY reached values significantly higher than what NICE usually recommend interventions.

Economic evidence statements

Dymond 2021 is a cost utility study comparing ospemifene plus SoC to SoC alone in post-menopausal women with VVA who were contraindicated for oestrogen based treatments. SoC consisted of over-the-counter non-hormonal moisturisers and lubricants. The study takes a UK (Scotland) NHS & Personal Social Services (PSS) perspective and reports outcomes in terms of QALYs.

NICE 2023 is a bespoke economic model developed to inform this guideline. It is a cost utility analysis, reporting outcomes in QALYs and taking a UK NHS & PSS perspective. It

included all women with bothersome genitourinary symptoms associated with the menopause and assumed they were not contraindicated for any interventions considered. The model compares estradiol, estriol, prasterone, ospemifene and laser to non-hormonal moisturisers and lubricants.

Both studies sourced utility scores from the same study, conducted in the population under consideration using the EQ-5D and scored using UK general population tariffs, NICE's preferred measure of utility.

Dymond 2021 found ospemifene to be cost effective compared to non-hormonal moisturisers and lubricants when a threshold of £20,000 per additional QALY was considered with a probability estimated at 89% of being the preferred option. This conclusion was robust to all sensitivity analyses undertaken.

NICE 2023 found estriol to be the preferred option with a 60% probability and the highest incremental net monetary benefit (INMB) of £346 with a threshold of £20,000 per QALY gained. This was robust to sensitivity analysis other than when the time horizon was extended to 10 years and effect assumed to remain (where laser became the preferred option). When only interventions relevant to people contraindicated for oestrogen was assumed prasterone became the preferred option.

Both studies were directly applicable to the review question given their perspective and elicitation of utility values discussed above. NICE 2023 was deemed to have minor limitations whilst Dymond 2021 had potentially serious limitations given the limited evidence used in estimating effectiveness.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Vulvovaginal dryness, pain with sex (dyspareunia), vulvovaginal discomfort/irritation, discomfort or pain when urinating (dysuria), and discontinuation of treatment due to side effects of treatment were prioritised as critical outcomes by the committee. These outcomes were identified as critical because they were defined by the Core Outcomes in Menopause (COMMA) global initiative (Lensen 2021). These outcomes are standardised and have been established as priorities by women seeking effective treatments, their clinicians, and researchers in this field.

The committee agreed that change in most bothersome symptom, distress, bother or interference of genitourinary symptoms, and satisfaction with treatment were important outcomes. The committee agreed that if evidence was identified for the critical outcomes, evidence for the important outcomes was not required.

The quality of the evidence

The NMAs allowed estimation of relative effects in terms of vulvovaginal dryness, pain with sex, vulvovaginal discomfort/irritation, or discontinuation due to adverse effects between all pairs of treatments for which RCT evidence was available, via direct and indirect comparisons, without breaking the rules of randomisation. The network for discomfort or pain when urinating (dysuria) was disconnected and NMA was not possible, instead pairwise meta-analysis was done for this outcome.

Analysis was done for the critical outcomes only as per the review protocol which stated that if NMA could be done for the critical outcomes then the secondary (important) outcomes would not be analysed.

GRADE was not undertaken for this review question. Instead, we intended to perform threshold analysis to explore how much the NMA evidence would need to change for the

recommendations made by the committee to change. Of the treatments that were explored in sufficiently large numbers of patients, efficacies were very similar, with no clear “best” treatment. Even in interventions with smaller numbers, the intervention which was estimated as “best” (laser) was not recommended outside of research given its larger cost made in not cost effective at conventional NICE thresholds. Changes of the ranking of interventions in the NMA therefore may not necessarily translate to changes in the recommendations made and therefore threshold analysis solely around the NMA results would not be useful for decision making and was not undertaken. The robustness of the recommendations to changes in the NMA results and other model inputs were explored as part of the economic model on this topic. The sensitivity of recommendations to effect estimates and the plausibility that future research reducing imprecision may demonstrate the needed change are discussed as part of the economic modelling.

Changes in the effectiveness evidence for the interventions of most interest in the NMA were explored during sensitivity analysis in the bespoke economic model based on the NMA. Given the importance of cost effectiveness in informing these recommendations and more widely within NICE this was seen as a more holistic way of exploring the changes in the effectiveness evidence. This is discussed in ‘Cost effectiveness and resource use’ below and more widely in the economic report.

For each of the outcomes the potential for small study bias was evaluated. Bias was assumed in comparisons of active interventions versus inactive control, and no bias was assumed between inactive control comparisons, as well as between active intervention comparisons. Bias-adjusted NMA models were compared to base-case consistency models using the Deviance Information Criterion (DIC). If the bias-adjusted model had a DIC that was lower by ≥5 then results from this were reported over the unadjusted model.

There was no evidence of bias due to small study effects for vulvovaginal dryness, pain with sex, vulvovaginal discomfort/irritation, or discontinuation due to adverse effects.

Heterogeneity was moderate for pain with sex and vulvovaginal dryness and low for vulvovaginal discomfort/irritation and discontinuation due to adverse effects. Following consideration of the inconsistency and heterogeneity in the evidence, the committee felt confident to make recommendations based on the NMA and the guideline economic analysis that was informed by the NMA.

The committee noted the strengths and limitations of the NMA when interpreting the results and did not rely solely on each treatment’s ranking in the NMA. However, they agreed to make strong recommendations despite the uncertainty and limitations in the evidence, as the clinical evidence was strong for some treatments and supported by economic evidence. Where there was a more limited evidence base, the committee decided to make weaker (‘consider’) recommendations, which were supported by their clinical experience.

Benefits and harms

The committee discussed that there are specific considerations for people with a history of breast cancer who have genitourinary symptoms associated with the menopause (see evidence review B1). So, they made specific recommendations related to people with no history of breast cancer and some overarching recommendations for people regardless of whether or not they have a history of breast cancer.

Women, trans men, and non-binary people registered female at birth with no history of breast cancer

The committee discussed the evidence from the network meta-analysis (NMA). They noted that vaginal oestrogen (particularly oestriol but also oestradiol) was effective in reducing vaginal dryness and pain with sex. Oestradiol also showed effectiveness in

reducing vulvovaginal discomfort/irritation. Furthermore, the bespoke economic model conducted for this review showed that vaginal oestrogen was cost-effective. Whilst there were some differences between preparations in its effectiveness for certain symptoms, they agreed that overall, there was a lot of overlap in confidence intervals making it unlikely that no one type of vaginal preparation would be more effective than another. They concluded that vaginal oestrogen preparations (conjugated oestrogen, oestradiol and oestriol) as local cream, gel, tablet, pessary and ring should be offered for genitourinary symptoms so that people could choose their preferred option. There was limited evidence on longer-term use of vaginal oestrogens, and most trials had follow-up of 12 weeks only. However, the committee agreed that systemic absorption of oestrogen is relatively low with vaginal oestrogen so it would likely be safe to continue treatment for as long as needed to relieve symptoms. To gain a better understanding about longer term follow-up to inform future updates the committee also prioritised this topic for a research recommendation (for details see Appendix K)

Vaginal oestrogen was well tolerated, as the evidence showed that discontinuation due to adverse events was not significant. The committee agreed that this was consistent with their experience and was also in line with advice from the MHRA drug safety update on hormone replacement therapy (2019). Although discontinuation due to adverse effects are rare, the committee agreed that the person should also be made aware that symptoms often return when treatment is stopped, so they may decide to start using vaginal oestrogen again if the symptoms remain bothersome. The committee also decided that it was important to discuss with the person that some oestrogen is absorbed into the blood stream but this generally is much less than systemic HRT. They agreed to highlight this because the low absorption means that there is therefore no requirement to combine low dose vaginal oestrogens with systemic progestogen treatment for protection against endometrial hyperplasia and cancer. The committee agreed that all postmenopausal women should seek medical advice from their GP if they have vaginal bleeding since it is a common side effect within the first 3 months of treatment. They can then seek advice and if needed have further investigations to ascertain the cause of the bleeding.

The committee noted that it is common clinical practice to prescribe the smallest effective dosage to balance the risks and benefits of a treatment and made an overarching recommendation related to this for HRT (including vaginal oestrogen). So, they highlighted this as a general principle when starting HRT. Effectiveness can vary between people, so starting with the lowest effective dosage can help find the right balance between effectively treating symptoms and risks from the treatment, taking into account each person's specific needs.

There was some discussion about how to manage troublesome GU symptoms that persist despite using vaginal oestrogen. There was no evidence in the NMA that related to this that the committee could draw on. However, some committee members discussed that increasing the dose within the therapeutic range may be helpful, and all committee members agreed that increasing the dose of vaginal oestrogen beyond the standard therapeutic range may be unsafe. They therefore agreed increasing dosage should only be done after seeking advice from a healthcare professional with expertise in menopause, who would be able to see whether an increased dose is the best option for the person or whether alternative treatments ought to be offered.

Based on their knowledge and experience the committee discussed that non-hormonal vaginal moisturisers and lubricants could be considered for people in whom local vaginal oestrogen is contraindicated or who would prefer not to take up this treatment option. The NMA suggested that these were less effective than vaginal oestrogens and whilst the point estimate was on the effective side for vulvovaginal dryness, pain with sex and vulvovaginal discomfort/irritation the confidence interval crossed the line of no effect. They noted that these were less often discontinued due to adverse events than other options (such as prasterone, oestriol, or oestradiol), suggesting that when it worked for a person

they felt comfortable to keep using it. Whilst the evidence highlighted uncertainty about the effectiveness of these treatments, based on their experience the committee decided that moisturisers and lubricants could be tried when local vaginal oestrogen is contraindicated or not preferred.

The committee also discussed the role of prasterone and ospemifene in the management of troublesome genitourinary symptoms. The noted that both of these are more expensive than vaginal oestrogen or moisturisers and lubricants. However, the NMA showed them to be effective in reducing vulvovaginal dryness and pain with sex but not vulvovaginal discomfort/irritation. They were also not significantly discontinued due to adverse events.

In relation to prasterone, the economic model showed it not to be a cost effective strategy when compared to vaginal oestrogen, moisturisers and lubricants for all people with troublesome genitourinary symptoms. However, given its clinical effectiveness, the committee discussed that prasterone could be offered when other treatments (vaginal oestrogen, moisturisers or lubricants) have been ineffective or not tolerated and troublesome genitourinary symptoms persist.

Regarding ospemifene the committee noted that it was a more expensive option and that the economic model, similarly to prasterone, showed it not to be cost effective for all people as a first line option compared to vaginal oestrogen, moisturisers and lubricants. An advantage of ospemifene is that it is an oral treatment which means that it is suitable for those who would find local application difficult (for example due to disability). They therefore only recommended ospemifene if locally applied treatments are impractical.

All women, trans men, and non-binary people registered female at birth

The committee noted that some of their recommendations applied to all women, trans men, and non-binary people registered female at birth including those with a history of breast cancer (as covered by evidence review B2).

The committee was aware that many people seem to adjust vaginal oestrogen dosages by themselves and that this is not always safe. While they thought it is relatively uncommon that people do not tolerate vaginal oestrogen, they noted it can happen. They also noted the common side effect of vaginal bleeding in the first 3 months of use and that medical advice is needed when this happens. To address this, the committee referred to the relevant recommendation on reviewing treatments at 3 and 12 months (which was a recommendation made in 2015).

The committee thought that there was a lack of awareness that moisturisers or lubricants can be used alone or in addition to vaginal oestrogen and the committee therefore suggested that this information should be shared with the person.

The committee discussed laser treatment which ranked highly in the NMA and was effective in reducing vulvovaginal dryness and pain with sex but not vulvovaginal discomfort/irritation and there was too little information on discontinuation due to adverse events. However, they were not confident about those findings because the trials were small, some had some design limitations (baseline differences between arms and studies not reporting all outcomes) and they also noted that there were conflicts of interests due to sponsorship by industry. They also agreed that there was potential for harm of this treatment if not conducted appropriately (for example scarring). The costs associated with lasers meant that despite showing clinical effectiveness, the health economic model indicated that laser treatment was not a cost effective option and would be associated additionally with a large resource impact. The committee noted these limitations of the evidence and thought these were in line with concerns raise in the NICE IPG697 for transvaginal laser therapy for urogenital atrophy. They therefore recommended against the use of laser for troublesome genitourinary symptoms unless as part of a randomised controlled trial. Given the relatively small evidence base related to this they also agreed to

make a research recommendation on vaginal laser treatment for genitourinary symptoms associated with menopause (see Appendix K).

The committee agreed that the evidence on the outcome pain/discomfort when urinating was insufficient and inconclusive and therefore did not make any recommendations based on this data.

Cost effectiveness and resource use

The committee highlighted that the 1 economic evaluation identified and the bespoke economic model developed for this guideline were directly relevant to the decision problem. The bespoke model considered all interventions of interest and effectiveness inputs were based on the accompanying NMA and interpretation of economic outcomes could be considered alongside the outcomes from the clinical evidence review. The identified economic evaluation only considered ospemifene and lubricants and moisturisers and was informed by a subset of the trials identified for inclusion in the NMA. The bespoke economic model was therefore relied upon more heavily to inform considerations around resource use and cost effectiveness.

Based on the economic model the committee recommended vaginal oestrogen preparations (estriol and estradiol) as these interventions had a greater than 60% probability of being the preferred option in the economic model. This was also underpinned by strong clinical evidence from the NMA and the committee's opinion and experience that these were effective and safe treatments. The committee decided against differentiating between estriol and estradiol in the recommendations even though estriol was likely to be the more cost effective intervention. The committee highlighted that the cost of both interventions were very similar and the difference in probability in the probabilistic sensitivity analysis was being driven by the slightly lower cost of estriol. Estradiol was also available without a prescription which may appeal to some users (and was preferred over estriol when the cost was borne by the individual rather than the NHS). The NMA also suggested that estradiol may be more effective for discomfort than estriol, an NMA outcome which did not inform the economic model. This recommendation will lead to a resource impact if women initiate oestrogen based treatments earlier rather than trying non-hormonal moisturisers and lubricants first but as discussed there was strong clinical and cost effectiveness evidence that this would be an efficient use of NHS resources.

Non-hormonal moisturisers and lubricants were also recommended for women where local vaginal oestrogen was contraindicated or where the individual preferred not to use it. Even though lubricants and moisturisers were ranked lower than prasterone (in terms of preferred options) and ospemifene the committee decided to recommend them as they have a lower unit cost than other interventions considered, can be used alongside other treatments, and are often used by people as it can be readily purchased without the need for a GP or pharmacist visit. The NMA also highlighted that discontinuation due to adverse events was lower than for other treatments considered and therefore represented a convenient treatment with limited adverse events and was likely to be widely used, early in the treatment pathway, regardless of recommendations made. It should be noted though that non-hormonal moisturisers and lubricants could lead to out-of-pocket expenses for the individual if bought over the counter which could cause inequity. The committee therefore did not recommend them first line.

Prasterone was the preferred option for those who were contraindicated or wished not to take local vaginal oestrogen. It was strongly preferred to ospemifene in the base-case of the economic model although the preference was much weaker if a gynaecology outpatient visit was not needed for ospemifene. Prasterone was recommended by the committee as a second-line treatment when vaginal oestrogens and non-hormonal

moisturisers and lubricants had been ineffective, are not tolerated or were otherwise unsuitable.

Ospemifene was recommended by the committee if locally applied treatments were impractical for example because of disability. The committee acknowledged that this somewhat went against the conclusions of the economic evaluation identified in the evidence review but highlighted that the study did not consider prasterone as a potential alternative treatment in this group unlike the bespoke economic model. Prasterone was both less expensive and more effective than ospemifene in the bespoke economic model and thus was the preferred option for those that were contraindicated or wished not to take local oestrogen. The committee did recommend ospemifene for the above group as no alternative treatments were identified for this group and the alternative would have been no treatment. The committee considered that not recommending ospemifene for this group would lead to inequalities in receiving treatment.

Lasers despite being estimated as the most effective treatment in the economic model were also associated with the largest costs. It was very unlikely that laser is a cost effective option with it only becoming the preferred option at thresholds above £270,000 per QALY gained, significantly above the thresholds at which NICE typically recommend interventions. Laser was the preferred option when more favourable assumptions around costs and longevity of effectiveness were assumed but there was considerable uncertainty around how plausible these assumptions were. The committee also highlighted uncertainty about how the estimated costs were relevant for the NHS who may be able to exploit economies of scale and reduce costs. It was also unclear who would administer the treatment. Given these uncertainties in the economic model, uncertainty around the applicability of the effect size estimated in the NMA and informing the model as well as the potential large resource impact from providing laser on the NHS for troublesome genitourinary symptoms the committee decide against recommending it outside of a randomised controlled trial.

Other factors the committee took into account

The committee were aware that overactive bladder can co-occur with genitourinary menopause symptoms and that vaginal oestrogen can be given in these circumstances. The committee acknowledged that this was recommended in the NICE guideline on urinary incontinence and pelvic organ prolapse in women: management, which was cross referred to in the Menopause guideline in the section for people with no history of breast cancer. This was because the committee did not recommend vaginal oestrogen for people with a history of breast cancer as a first line option.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.19 to 1.4.25, 1.4.31 to 1.4.33 and 1.5.2 as well as research recommendation 3 (on longer term safety of vaginal oestrogen) as well as research recommendation 5 (on vaginal laser treatment for genitourinary symptoms) in the NICE guideline.

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1

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Table 13: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022362133
1.	Review title	Treatments for managing genitourinary symptoms associated with the menopause.
2.	Review question	What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?
3.	Objective	To determine if localised oestrogens, ospemifene, prasterone and transvaginal laser therapy are effective in treating genitourinary symptoms.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE ePub Ahead-of-Print and MEDLINE-in-Process • Epistemonikos • INAHTA • HTA via CRD Searches will be restricted by: • Date limitations (2015 to date) for interventions included in the original searches. No date limit for interventions not included in the original search (Transvaginal Laser Therapy and Prasterone) • English language

ID	Field	Content
		• Human studies • RCTs and Systematic Reviews • Conference abstracts will be excluded from the search results The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Genitourinary symptoms associated with the menopause.
6.	Population	Inclusion: Women with troublesome genitourinary symptoms associated with the menopause. Exclusion: No additional exclusion criteria

7.	Intervention	We will categorise interventions into classes (each main bullet represents one class):
		• Vaginal oestrogens
		  ○ Estriol cream
		  ○ Estriol pessary (doses 30, 40, 50, 100 micrograms)
		  ○ Estriol gel
		  ○ Estradiol vaginal tablet/pessary
		  ○ Estradiol Ring
		  ○ Estradiol gel
		  ○ Estradiol soft-gel capsule
		• Selective oestrogen receptor modulators
		  ○ Ospemifene
		• Dehydroepiandrosterone
		  ○ Prasterone pessary
		• Transvaginal laser therapy

ID	Field	Content
		○ CO2 laser ○ Erbium laser • Non hormonal local treatments ○ Moisturisers and lubricants
8.	Comparator	• Other active treatment • Placebo or sham treatment ○ Topical creams and gels ○ Tablets / pessaries ○ Sham laser ○ Ring • No treatment
9.	Types of study to be included	Include published English language, full-text papers: • Systematic reviews of RCTs • RCTs
10.	Other exclusion criteria	Conference abstracts will be excluded For network meta-analysis (NMA): Active interventions that are not part of the decision problem will not be considered in the analysis, unless they act as the sole connectors of the interventions of interest in the network.
11.	Context	This review will update NG23
12.	Primary outcomes (critical outcomes)	• vulvovaginal dryness • pain with sex (dyspareunia) • vulvovaginal discomfort or irritation • discomfort or pain when urinating (dysuria)

ID	Field	Content
		• discontinuation of treatment due to side effects
13.	Secondary outcomes (important outcomes)	• change in most bothersome symptom • distress, bother or interference of genitourinary symptoms • satisfaction with treatment
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on all records. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Quantitative findings will be formally summarised in the review. For pair-wise meta-analysis, where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. If NMA is possible it will be done for primary outcomes only and separate pair-wise meta-analyses will not be done for secondary outcomes. NMA will be conducted within a Bayesian framework using Markov Chain Monte Carlo simulation techniques in WinBUGS. Non-informative priors will be initially used. Two chains with different

ID	Field	Content
		initial values will be run simultaneously. Convergence will be assessed by inspecting the mixing of chains and the Brooks Gelman-Rubin diagram. We will also measure the ranking of treatments on each outcome. The goodness of fit of each model will be tested by comparing the posterior mean of the residual deviance, the deviance information criterion and the posterior median between-study standard deviation. Inconsistency between direct and indirect evidence will be explored by comparing the fit of a model assuming consistency with a model allowing for inconsistency. If potential inconsistency is identified, further node-split tests will be conducted. If NMA is not possible then fixed effect pair-wise meta-analysis will be conducted will be conducted for the primary and secondary outcomes and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: • Serious intervention-related adverse effects: statistical significance • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous

ID	Field	Content	
		outcomes ; +/- 0.5x control group SD for continuous outcomes How the evidence included in NG23 will be incorporated with the new evidence: Studies meeting the current protocol criteria and previously included in the NG23 will be included in this update. The methods for quantitative analysis (data extraction, risk of bias, strategy for data synthesis, and analysis of subgroups) will be the same as for the new evidence and as outlined in this protocol.	
17.	Analysis of sub-groups	Evidence will not be stratified) Evidence will be subgrouped for pairwise meta-analysis by the following only in the event that there is significant heterogeneity in outcomes: • Duration of treatment Groups identified in the equality considerations section of the scope: • Age • Disability • Ethnicity • Socioeconomic status • non-binary and trans-masculine people. Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery

ID	Field	Content		
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	07 October 2022		
22.	Anticipated completion date	23 August 2023		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact Senior Systematic Reviewer 5b Named contact e-mail menopause@nice.org.uk 5e Organisational affiliation of the review Guideline development group NGA, National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline development group NGA, National Institute for Health and Care Excellence (NICE): • Senior Systematic Reviewer • Systematic Reviewer		

ID	Field	Content	
26.	Funding sources/sponsor	This systematic review is being completed by NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details	None	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=362133	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Dehydroepiandrosterone; Estrogens; Female; Humans; Laser Therapy; Menopause; Ospemifene	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing

ID	Field	Content	
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CO2: carbon dioxide; CRD: Centre for Reviews and Dissemination; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; INAHTA: International Network of Agencies for Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Clinical searches

Database: Ovid MEDLINE(R) ALL <1946 to August 12, 2022>

Date of last search: 15/08/2022

#	Searches	
1	Climacteric/	4933
2	Menopause/ or Perimenopause/ or Postmenopause/	56026
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102480
4	("change of life" or life change?).tw.	3151
5	or/1-4	116632
6	Vagina/ or Vulva/	42244
7	Atrophy/	33673
8	Pruritus/ or Pruritus Vulvae/	13555
9	Dehydration/	14305
10	or/7-9	61475
11	6 and 10	985
12	exp Female Urogenital Diseases/	1263271
13	(vulvovagini* or vaginitis).tw.	4848
14	((vagina? or vulva? or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) adj4 (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspar?euni? or dysuri? or discharge? or discomfort* or uncomfortable* or erosion or eroded or thin*)).tw.	12069
15	VVA.tw.	458
16	(labia* adj4 (adhesi* or fus*)).tw.	408
17	((vagina? or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) adj4 (syndrome? or symptom? or indication? or issue? or problem? or condition?)).tw.	6219
18	GSM.tw.	1837
19	Dyspareunia/	2394
20	Sexual Dysfunction, Physiological/	10306
21	((sex* or intercourse) adj4 (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)).tw.	162827
22	or/11-21	1426199
23	exp Estrogens/	167321
24	Estrogen Replacement Therapy/	15497
25	(estrogen* or oestrogen*).tw.	170307
26	Estradiol/ or Estriol/	88845
27	(estradiol or estriol or oestradiol or oestriol).tw.	101327
28	"Estrogens, Conjugated (USP)"/	3668
29	exp Selective Estrogen Receptor Modulators/	29221
30	(selective adj (oestrogen or estrogen) adj receptor? modulator?).tw.	3619
31	SERM?.tw.	2351
32	or/23-31	302534
33	Administration, Intravaginal/ or Administration, Topical/	45428
34	"Vaginal Creams, Foams, and Jellies"/	1367
35	Gels/ or Pessaries/ or Suppositories/	36225
36	(local* or topical* or intravaginal* or intra-vaginal* or vaginal* or low-dose* or low-dosage*).tw.	1805086
37	(vagina* adj4 (cream? or gel? or pessar* or ring? or tablet? or capsule? or suppositor* or ovule?)).tw.	4466
38	vagitori*.tw.	14

#	Searches	
39	or/33-38	1847930
40	32 and 39	29753
41	(gynest or "ortho-gynest" or ovestin or imvaggis or blissel or vagifem or vagirux or estring or vaginal ring? or femring or estrace or premarin).tw.	1727
42	Dienestrol/	187
43	Estrogens, Non-Steroidal/	3355
44	(dienestrol or synestrol or dienoestrol or oestrasid).tw.	328
45	(ospemifene or osphena or ophena or senshio).tw.	204
46	or/41-45	5643
47	40 or 46	34260
48	5 and 22 and 47	2576
49	limit 48 to yr="2015 -Current"	738
50	exp Dehydroepiandrosterone/	12040
51	DHEA?.tw.	9181
52	(prasterone or dehydroepiandrosterone or dehydroisoandrosterone or androstenolone or dha sulfate or intrarosa).tw.	13049
53	or/50-52	18413
54	Lasers/ or Lasers, Gas/ or Lasers, Solid-State/	49006
55	Low-Level Light Therapy/ or Laser Therapy/	46594
56	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or endovaginal* or vagina* or procedure*) adj4 (laser* or lazer*)).tw.	53723
57	((CO2 or YAG or ER:YAG or erbium?) adj4 (laser? or lazer?)).tw.	14870
58	(SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*).tw.	25
59	or/54-58	116699
60	53 or 59	135079
61	5 and 22 and 60	709
62	49 or 61	1311
63	letter/	1190200
64	editorial/	614990
65	news/	213790
66	exp historical article/	408719
67	Anecdotes as Topic/	4746
68	comment/	975150
69	case report/	2285443
70	(letter or comment*).ti.	179670
71	or/63-70	4790027
72	randomized controlled trial/ or random*.ti,ab.	1470708
73	71 not 72	4759251
74	animals/ not humans/	5002654
75	exp Animals, Laboratory/	942570
76	exp Animal Experimentation/	10210
77	exp Models, Animal/	631738
78	exp Rodentia/	3475903
79	(rat or rats or mouse or mice).ti.	1408417
80	or/73-79	10634053
81	62 not 80	1147
82	limit 81 to english language	1094
83	Meta-Analysis/	165590
84	Meta-Analysis as Topic/	21618
85	(meta analy* or metanaly* or metaanaly*).ti,ab.	243080
86	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.	301948
87	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	51395
88	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	73837
89	(search* adj4 literature).ab.	88021

#	Searches	
90	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	323059
91	cochrane.jw.	16095
92	or/83-91	606821
93	randomized controlled trial.pt.	574945
94	controlled clinical trial.pt.	94985
95	pragmatic clinical trial.pt.	2132
96	randomi#ed.ab.	683662
97	placebo.ab.	230809
98	drug therapy.fs.	2520040
99	randomly.ab.	389092
100	trial.ab.	612284
101	groups.ab.	2393457
102	or/93-101	5452460
103	Clinical Trials as topic.sh.	200255
104	trial.ti.	268312
105	or/93-97,99,103-104	1509896
106	92 or 105	1971159
107	82 and 106	382

1

2 Database: Embase <1974 to 2022 August 12>

3 Date of last search: 15/08/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8931
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	133669
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	147870
4	("change of life" or life change?).tw.	4239
5	or/1-4	183310
6	vagina atrophy/	2824
7	vaginal dryness/	3359
8	female genital pruritus/ or vaginal pruritus/ or vulva pruritus/	1982
9	exp vaginitis/	16800
10	vagina bleeding/ or "vagina discharge (disease)"/ or vagina pain/ or vaginal burning sensation/ or vaginal discomfort/ or vaginal injury/ or vulvovaginal discomfort/	21392
11	genital system disease/ or genital bleeding/ or genital edema/ or genital injury/ or genital pain/ or genital pruritus/ or genital tract infection/ or genital tract inflammation/ or female genital tract inflammation/ or gynecologic disease/	23090
12	urogenital tract disease/ or urogenital tract inflammation/ or urogenital tract injury/ or urogenital tract infection/	12128
13	(vulvovagini* or vaginitis).tw.	5499
14	((vagina? or vulva? or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) adj4 (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspar?euni? or dysuri? or discharge? or discomfort* or uncomfortable* or erosion or eroded or thin*)).tw.	18831
15	VVA.tw.	747
16	(labia* adj4 (adhesi* or fus*)).tw.	573
17	((vagina? or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) adj4 (syndrome? or symptom? or indication? or issue? or problem? or condition?)).tw.	9704
18	menopause related disorder/ or menopausal syndrome/	9680
19	GSM.tw.	2588
20	Dyspareunia/	11728
21	sexual dysfunction/ or female sexual dysfunction/	32204
22	((sex* or intercourse) adj4 (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)).tw.	217511
23	or/6-22	332248

#	Searches	
24	exp estrogen/	289249
25	estrogen therapy/	23197
26	(estrogen* or oestrogen*).tw.	210294
27	(estradiol or estriol or oestradiol or oestriol).tw.	119334
28	selective estrogen receptor modulator/	8424
29	(selective adj (oestrogen or estrogen) adj receptor? modulator?).tw.	4891
30	SERM?.tw.	3574
31	or/24-30	399278
32	intravaginal drug administration/ or topical drug administration/	90384
33	vagina ring/ or vagina pessary/	5467
34	agents used intravaginally/	335
35	(local* or topical* or intravaginal* or intra-vaginal* or vaginal* or low-dose* or low-dosage*).tw.	2302572
36	(vagina* adj4 (cream? or gel? or pessar* or ring? or tablet? or capsule? or suppositor* or ovule?)).tw.	6600
37	vagitori*.tw.	14
38	or/32-37	2347980
39	31 and 38	43396
40	(gynest or "ortho-gynest" or ovestin or imvaggis or blissel or vagifem or vagirux or estring or vaginal ring? or femring or estrace or premarin).tw.	5671
41	Dienestrol/	667
42	(dienestrol or synestrol or dienoestrol or oestrasid).tw.	273
43	(ospemifene or osphena or ophena or senshio).tw.	346
44	or/40-43	6653
45	39 or 44	48126
46	5 and 23 and 45	4233
47	limit 46 to yr="2015 -Current"	1451
48	prasterone/	15972
49	DHEA?.tw.	12813
50	(prasterone or dehydroepiandrosterone or dehydroisoandrosterone or androstenolone or dha sulfate or intrarosa).tw.	14771
51	or/48-50	24822
52	laser/ or carbon dioxide laser/ or gas laser/ or exp YAG laser/ or gynecologic laser/	112577
53	low level laser therapy/ or laser therapy/	28558
54	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or endovaginal* or vagina* or procedure*) adj4 (laser* or lazer*)).tw.	66515
55	((CO2 or YAG or ER:YAG or erbium?) adj4 (laser? or lazer?)).tw.	18531
56	(SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*).tw.	63
57	or/52-56	167987
58	51 or 57	192710
59	5 and 23 and 58	1309
60	47 or 59	2456
61	letter.pt. or letter/	1242118
62	note.pt.	902286
63	editorial.pt.	733855
64	case report/ or case study/	2837266
65	(letter or comment*).ti.	224249
66	or/61-65	5463927
67	randomized controlled trial/ or random*.ti,ab.	1929806
68	66 not 67	5409192
69	animal/ not human/	1160145
70	nonhuman/	6987431
71	exp Animal Experiment/	2877258
72	exp Experimental Animal/	770928
73	animal model/	1572919
74	exp Rodent/	3852593

#	Searches	
75	(rat or rats or mouse or mice).ti.	1557433
76	or/68-75	14187550
77	60 not 76	1887
78	limit 77 to english language	1784
79	(conference abstract or conference paper or conference proceeding or "conference review").pt.	5268036
80	78 not 79	1184
81	systematic review/	363100
82	meta-analysis/	253228
83	(meta analy* or metanaly* or metaanaly*).ti,ab.	310677
84	((systematic or evidence) adj2 (review* or overview*)).ti,ab.	355558
85	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	62611
86	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	88350
87	(search* adj4 literature).ab.	110534
88	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	393126
89	((pool* or combined) adj2 (data or trials or studies or results)).ab.	85141
90	cochrane.jw.	23657
91	or/81-90	855740
92	random*.ti,ab.	1820226
93	factorial*.ti,ab.	44429
94	(crossover* or cross over*).ti,ab.	119290
95	((doubl* or singl*) adj blind*).ti,ab.	259833
96	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1185527
97	crossover procedure/	71153
98	single blind procedure/	47146
99	randomized controlled trial/	721862
100	double blind procedure/	197531
101	or/92-100	2710142
102	91 or 101	3308518
103	80 and 102	425

1

2 Database: Cochrane Database of Systematic Reviews (CDSR) Issue 8 of 12, August 2022

3 Date of last search: 15/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	443
7	{or #1-#6}	28528
8	MeSH descriptor: [Vagina] this term only	1411
9	MeSH descriptor: [Vulva] this term only	111
10	#8 or #9	1462
11	MeSH descriptor: [Pruritus] this term only	1427
12	MeSH descriptor: [Pruritus Vulvae] this term only	9
13	MeSH descriptor: [Dehydration] this term only	593
14	{or #11-#13}	2028
15	#10 and #14	8
16	MeSH descriptor: [Female Urogenital Diseases] explode all trees	43972
17	(vulvovagini* or vaginitis):ti,ab	782
18	((vagina? or vulva? or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary)	2663

#	Searches	
	near/4 (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspareuni? or dysuri? or discharge? or discomfort* or uncomfortable* or erosion or eroded or thin*)):ti,ab	
19	(VVA):ti,ab	175
20	(labia* near/4 (adhesi* or fus*)):ti,ab	8
21	((vagina? or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) near/4 (syndrome? or symptom? or indication? or issue? or problem? or condition?)):ti,ab	1855
22	(GSM):ti,ab	213
23	MeSH descriptor: [Dyspareunia] this term only	227
24	MeSH descriptor: [Sexual Dysfunction, Physiological] this term only	525
25	((sex* or intercourse) near/4 (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)):ti,ab	13862
26	{or #15-#25}	60093
27	MeSH descriptor: [Estrogens] explode all trees	1954
28	MeSH descriptor: [Estrogen Replacement Therapy] this term only	2124
29	(estrogen* or oestrogen*):ti,ab	12608
30	MeSH descriptor: [Estradiol] this term only	4455
31	MeSH descriptor: [Estriol] this term only	222
32	(estradiol or estriol or oestradiol or oestriol):ti,ab	9690
33	MeSH descriptor: [Estrogens, Conjugated (USP)] this term only	1017
34	MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees	415
35	(selective near (oestrogen or estrogen) near receptor? modulator?):ti,ab	530
36	SERM?:ti,ab	311
37	{or #27-#36}	20708
38	MeSH descriptor: [Administration, Intravaginal] this term only	1523
39	MeSH descriptor: [Administration, Topical] this term only	6570
40	MeSH descriptor: [Vaginal Creams, Foams, and Jellies] this term only	419
41	MeSH descriptor: [Gels] this term only	2419
42	MeSH descriptor: [Pessaries] this term only	207
43	MeSH descriptor: [Suppositories] this term only	620
44	(local* or topical* or intravaginal* or intra-vaginal* or vaginal* or low-dose* or low-dosage*):ti,ab	161126
45	(vagina* near/4 (cream? or gel? or pessar* or ring? or tablet? or capsule? or suppositor* or ovule?)):ti,ab	3253
46	vagitori*:ti,ab	8
47	{or #38-#46}	164414
48	#37 and #47	4526
49	(gynest or "ortho-gynest" or ovestin or imvaggis or blissel or vagifem or vagirux or estring or vaginal ring? or femring or estrace or premarin):ti,ab	970
50	MeSH descriptor: [Dienestrol] this term only	4
51	MeSH descriptor: [Estrogens, Non-Steroidal] this term only	71
52	(dienestrol or synestrol or dienoestrol or oestrasid):ti,ab	4
53	(ospemifene or osphena or ophena or senshio):ti,ab	85
54	{or #49-#53}	1131
55	#48 or #54	5271
56	#7 and #26 and #55	1000
57	"conference":pt or (clinicaltrials or trialsearch):so	608941
58	#56 not #57	643
59	#56 not #57 with Publication Year from 2015 to 2022, in Trials	186
60	#56 not #57 with Cochrane Library publication date Between Jan 2015 and Aug 2022, in Cochrane Reviews, Cochrane Protocols	12
61	MeSH descriptor: [Dehydroepiandrosterone] explode all trees	701
62	(DHEA?):ti,ab	1300
63	(prasterone or dehydroepiandrosterone or dehydroisoandrosterone or androstenolone or dha sulfate or intrarosa):ti,ab	1209
64	{or #61-#63}	1790
65	MeSH descriptor: [Lasers] this term only	687
66	MeSH descriptor: [Lasers, Gas] this term only	294

#	Searches	
67	MeSH descriptor: [Lasers, Solid-State] this term only	763
68	MeSH descriptor: [Low-Level Light Therapy] this term only	1162
69	MeSH descriptor: [Laser Therapy] this term only	2153
70	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or endovaginal* or vagina* or procedure*) near/4 (laser* or lazer*)):ti,ab	9740
71	((CO2 or YAG or ER?YAG or erbium?) near/4 (laser? or lazer?)):ti,ab	2821
72	(SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*):ti,ab	20
73	{or #65-#72}	12140
74	#64 or #73	13928
75	#7 and #26 and #74	193
76	"conference":pt or (clinicaltrials or trialsearch):so	608941
77	#75 not #76	80
78	#75 not #76 in Cochrane Reviews, Cochrane Protocols	4

1

2 Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7 of 12, July
3 2022

4 Date of last search: 15/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	443
7	{or #1-#6}	28528
8	MeSH descriptor: [Vagina] this term only	1411
9	MeSH descriptor: [Vulva] this term only	111
10	#8 or #9	1462
11	MeSH descriptor: [Pruritus] this term only	1427
12	MeSH descriptor: [Pruritus Vulvae] this term only	9
13	MeSH descriptor: [Dehydration] this term only	593
14	{or #11-#13}	2028
15	#10 and #14	8
16	MeSH descriptor: [Female Urogenital Diseases] explode all trees	43972
17	(vulvovagini* or vaginitis):ti,ab	782
18	((vagina? or vulva? or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) near/4 (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspareuni? or dysuri? or discharge? or discomfort* or uncomfortable* or erosion or eroded or thin*)):ti,ab	2663
19	(VVA):ti,ab	175
20	(labia* near/4 (adhesi* or fus*)):ti,ab	8
21	((vagina? or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) near/4 (syndrome? or symptom? or indication? or issue? or problem? or condition?)):ti,ab	1855
22	(GSM):ti,ab	213
23	MeSH descriptor: [Dyspareunia] this term only	227
24	MeSH descriptor: [Sexual Dysfunction, Physiological] this term only	525
25	((sex* or intercourse) near/4 (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)):ti,ab	13862
26	{or #15-#25}	60093
27	MeSH descriptor: [Estrogens] explode all trees	1954
28	MeSH descriptor: [Estrogen Replacement Therapy] this term only	2124
29	(estrogen* or oestrogen*):ti,ab	12608
30	MeSH descriptor: [Estradiol] this term only	4455
31	MeSH descriptor: [Estriol] this term only	222

#	Searches	
32	(estradiol or estriol or oestradiol or oestriol):ti,ab	9690
33	MeSH descriptor: [Estrogens, Conjugated (USP)] this term only	1017
34	MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees	415
35	(selective near (oestrogen or estrogen) near receptor? modulator?):ti,ab	530
36	SERM?:ti,ab	311
37	{or #27-#36}	20708
38	MeSH descriptor: [Administration, Intravaginal] this term only	1523
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40	MeSH descriptor: [Vaginal Creams, Foams, and Jellies] this term only	419
41	MeSH descriptor: [Gels] this term only	2419
42	MeSH descriptor: [Pessaries] this term only	207
43	MeSH descriptor: [Suppositories] this term only	620
44	(local* or topical* or intravaginal* or intra-vaginal* or vaginal* or low-dose* or low-dosage*):ti,ab	161126
45	(vagina* near/4 (cream? or gel? or pessar* or ring? or tablet? or capsule? or suppositor* or ovule?)):ti,ab	3253
46	vagitori*:ti,ab	8
47	{or #38-#46}	164414
48	#37 and #47	4526
49	(gynest or "ortho-gynest" or ovestin or imvaggis or blissel or vagifem or vagirux or estring or vaginal ring? or femring or estrace or premarin):ti,ab	970
50	MeSH descriptor: [Dienestrol] this term only	4
51	MeSH descriptor: [Estrogens, Non-Steroidal] this term only	71
52	(dienestrol or synestrol or dienoestrol or oestrasid):ti,ab	4
53	(ospemifene or osphena or ophena or senshio):ti,ab	85
54	{or #49-#53}	1131
55	#48 or #54	5271
56	#7 and #26 and #55	1000
57	"conference":pt or (clinicaltrials or trialsearch):so	608941
58	#56 not #57	643
59	#56 not #57 with Publication Year from 2015 to 2022, in Trials	186
60	#56 not #57 with Cochrane Library publication date Between Jan 2015 and Aug 2022, in Cochrane Reviews, Cochrane Protocols	12
61	MeSH descriptor: [Dehydroepiandrosterone] explode all trees	701
62	(DHEA?):ti,ab	1300
63	(prasterone or dehydroepiandrosterone or dehydroisoandrosterone or androstenolone or dha sulfate or intrarosa):ti,ab	1209
64	{or #61-#63}	1790
65	MeSH descriptor: [Lasers] this term only	687
66	MeSH descriptor: [Lasers, Gas] this term only	294
67	MeSH descriptor: [Lasers, Solid-State] this term only	763
68	MeSH descriptor: [Low-Level Light Therapy] this term only	1162
69	MeSH descriptor: [Laser Therapy] this term only	2153
70	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or endovaginal* or vagina* or procedure*) near/4 (laser* or lazer*)):ti,ab	9740
71	((CO2 or YAG or ER?YAG or erbium?) near/4 (laser? or lazer?)):ti,ab	2821
72	(SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*):ti,ab	20
73	{or #65-#72}	12140
74	#64 or #73	13928
75	#7 and #26 and #74	193
76	"conference":pt or (clinicaltrials or trialsearch):so	608941
77	#75 not #76	80
78	#75 not #76 in Trials	76

1

2 Database: Epistemonikos

1 Date of last search: 15/08/2022

#	Searches	
1	(menopau* OR postmenopau* OR perimenopau* OR climacteri* OR "change of life" OR "life change" OR "life changes")	
2	((vulvovagin* OR vaginitis OR VVA OR GSM OR (labia* AND (adhesi* or fus*))) OR ((vagina* OR vulva* OR (vulvo-vagina*) OR urogenital or genitourinary OR (genito-urinary)) AND (atroph* OR dry* OR prurit* OR sore* OR irrita* OR itch* OR inflam* OR pain* OR burn OR dyspareunia OR dysuria OR discharge* OR discomfort* OR uncomfortable* OR erosion OR eroded OR thin* OR syndrome* OR symptom* OR indication* OR issue* OR problem* OR condition*)) OR ((sex* OR intercourse) AND (pain* OR discomfort* OR bleed* OR blood* OR disorder* OR function* OR dysfunction* OR uncomfortable* OR alter* OR chang* OR differ* OR reduc*)))	
3	((estrogen* OR oestrogen* OR estradiol OR estriol OR oestradiol OR oestriol OR SERM* OR vagitori* OR gynest OR "ortho-gynest" or ovestin OR imvaggis OR blissel OR vagifem OR vagirux OR estring OR "vaginal ring" OR "vaginal rings" OR femring OR estrace OR premarin OR dienestrol OR synestrol OR dienoestrol OR oestrasid OR ospemifene OR osphena OR ophena OR senshio) OR (vagina* AND (cream* OR gel* OR pessar* OR ring* OR tablet* OR capsule* OR suppositor* OR ovule*)))	
4	1 AND 2 AND 3	
5	Limit 2015-2022	309

2 Date of last search: 15/08/2022

#	Searches	
1	(menopau* OR postmenopau* OR perimenopau* OR climacteri* OR "change of life" OR "life change" OR "life changes")	
2	((vulvovagin* OR vaginitis OR VVA OR GSM OR (labia* AND (adhesi* or fus*))) OR ((vagina* OR vulva* OR (vulvo-vagina*) OR urogenital or genitourinary OR (genito-urinary)) AND (atroph* OR dry* OR prurit* OR sore* OR irrita* OR itch* OR inflam* OR pain* OR burn OR dyspareunia OR dysuria OR discharge* OR discomfort* OR uncomfortable* OR erosion OR eroded OR thin* OR syndrome* OR symptom* OR indication* OR issue* OR problem* OR condition*)) OR ((sex* OR intercourse) AND (pain* OR discomfort* OR bleed* OR blood* OR disorder* OR function* OR dysfunction* OR uncomfortable* OR alter* OR chang* OR differ* OR reduc*)))	
3	((prasterone OR dehydroepiandrosterone OR dehydroisoandrosterone OR androstenolone OR (dha sulfate) OR intrarosa OR DHEA OR SMARTXIDE* OR IntimaLase* OR RenovaLase* OR Incontilase* OR Fotana*) OR ((treatment* OR device* OR therap* OR appl* OR fractional OR surg* OR scapel* OR (carbon dioxide*) OR (non-ablative) OR transvaginal* OR endovaginal* OR vagina* OR procedure* OR CO2 OR ERYAG OR "ER YAG" OR erbium*) AND (laser* OR lazer*)))	
4	1 AND 2 AND 3	148

3

4 Database: CRD HTA

5 Date of last search: 15/08/2022

#	Searches	
1	MeSH DESCRIPTOR climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR Postmenopause	209
5	((menopau* or postmenopau* or perimenopau* or climacteri*))	957
6	(("change of life" or "life change" or "life changes"))	38
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	994
8	MeSH DESCRIPTOR vagina	83
9	MeSH DESCRIPTOR vulva	6
10	MeSH DESCRIPTOR Atrophy	17
11	MeSH DESCRIPTOR Pruritus	34
12	MeSH DESCRIPTOR Pruritus Vulvae	0
13	MeSH DESCRIPTOR Dehydration	19
14	#8 OR #9	87
15	#10 OR #11 OR #12 OR #13	70
16	#14 AND #15	1
17	MeSH DESCRIPTOR Female Urogenital Diseases EXPLODE ALL TREES	4650
18	((vulvovagini* or vaginitis))	31
19	(((vagina* or vulva* or vulvovaginal or (vulvo-vaginal) or urogenital or genitourinary or (genito-urinary))	334

#	Searches	
	AND (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspareunia or dysuria or discharge* or discomfort* or uncomfortable* or erosion or eroded or thin*)))	
20	(VVA)	0
21	((labia* AND (adhesi* or fus*)))	1
22	(((vagina* or vulvovagina* or (vulvo-vagina*) or urogenital or genitourinary or (genito-urinary)) AND (syndrome* or symptom* or indication* or issue* or problem* or condition*)))	723
23	(GSM)	2
24	(((sex* or intercourse) AND (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)))	2053
25	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	6795
26	#7 AND #25	213
27	(#7 AND #25) IN HTA	29

1

2 Database: INAHTA

3 Date of last search: 15/08/2022

#	Searches	
1	"Climacteric"[mh] or "Menopause"[mh] or "Perimenopause"[mh] or "Postmenopause"[mh]	9
2	(menopau* or postmenopau* or perimenopau* or climacteri*)	117
3	("change of life" or "life change" or "life changes")	7
4	#3 OR #2 OR #1	209
5	"Vagina"[mh] or "Vulva"[mh]	957
6	"Atrophy"[mh]	38
7	"Pruritus"[mh] or "Pruritus Vulvae"[mh]	994
8	"Dehydration"[mh]	83
9	#8 OR #7 OR #6	6
10	#9 AND #5	17
11	"Female Urogenital Diseases"[mhe] or "Dyspareunia"[mh] or "Sexual Dysfunction, Physiological"[mh]	34
12	(vulvovagini* or vaginitis)	0
13	((vagina* or vulva* or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) AND (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspareunia or dysuria or discharge* or discomfort* or uncomfortable* or erosion or eroded or thin*))	19
14	(VVA)	87
15	((labia* AND (adhesi* or fus*)))	70
16	(((vagina* or vulvovagina* or (vulvo-vagina*) or urogenital or genitourinary or (genito-urinary)) AND (syndrome* or symptom* or indication* or issue* or problem* or condition*)))	1
17	(GSM)	4650
18	(((sex* or intercourse) AND (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)))	31
19	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	334
20	#7 AND #25	0
21	(#7 AND #25) IN HTA	1
22	(VVA)	723
23	((labia* AND (adhesi* or fus*)))	2
24	(((vagina* or vulvovagina* or (vulvo-vagina*) or urogenital or genitourinary or (genito-urinary)) AND (syndrome* or symptom* or indication* or issue* or problem* or condition*)))	2053
25	(GSM)	6795
26	(((sex* or intercourse) AND (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)))	213
27	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	29

4 **Economic searches**

5

6 Database: Ovid MEDLINE(R) ALL <1946 to July 27, 2022>

7 Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	55972
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102310
4	("change of life" or life change?).tw.	3141
5	or/1-4	116452
6	limit 5 to english language	103660
7	limit 6 to yr="2012 -Current"	41579
8	letter/	1188475
9	editorial/	613156
10	news/	213557
11	exp historical article/	408665
12	Anecdotes as Topic/	4746
13	comment/	973045
14	case report/	2282504
15	(letter or comment*).ti.	179095
16	or/8-15	4782431
17	randomized controlled trial/ or random*.ti,ab.	1466248
18	16 not 17	4751747
19	animals/ not humans/	4997958
20	exp Animals, Laboratory/	942090
21	exp Animal Experimentation/	10205
22	exp Models, Animal/	631246
23	exp Rodentia/	3472512
24	(rat or rats or mouse or mice).ti.	1407073
25	or/18-24	10620565
26	7 not 25	34368
27	Economics/	27455
28	Value of life/	5793
29	exp "Costs and Cost Analysis"/	259348
30	exp Economics, Hospital/	25612
31	exp Economics, Medical/	14359
32	Economics, Nursing/	4013
33	Economics, Pharmaceutical/	3074
34	exp "Fees and Charges"/	31172
35	exp Budgets/	14034
36	budget*.ti,ab.	33535
37	cost*.ti.	136425
38	(economic* or pharmaco?economic*).ti.	56592
39	(price* or pricing*).ti,ab.	48567
40	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	191586
41	(financ* or fee or fees).ti,ab.	145674
42	(value adj2 (money or monetary)).ti,ab.	2817
43	or/27-42	689907
44	exp models, economic/	16130
45	*Models, Theoretical/	64214
46	*Models, Organizational/	6490
47	markov chains/	15758
48	monte carlo method/	31445
49	exp Decision Theory/	12940
50	(markov* or monte carlo).ti,ab.	79077
51	econom* model*.ti,ab.	4760
52	(decision* adj2 (tree* or analy* or model*)).ti,ab.	31806
53	or/44-52	210296
54	43 or 53	865352

#	Searches	
55	26 and 54	849

Database: Embase <1974 to 2022 July 27>
Date of last search: 28/07/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8930
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	133601
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	147803
4	("change of life" or life change?).tw.	4239
5	or/1-4	183218
6	limit 5 to english language	163179
7	limit 6 to yr="2012 -Current"	81270
8	letter.pt. or letter/	1241876
9	note.pt.	901797
10	editorial.pt.	733613
11	case report/ or case study/	2836641
12	(letter or comment*).ti.	224206
13	or/8-12	5462442
14	randomized controlled trial/ or random*.ti,ab.	1928915
15	13 not 14	5407726
16	animal/ not human/	1159758
17	nonhuman/	6983755
18	exp Animal Experiment/	2874637
19	exp Experimental Animal/	770091
20	animal model/	1570755
21	exp Rodent/	3850325
22	(rat or rats or mouse or mice).ti.	1557060
23	or/15-22	14181910
24	7 not 23	61890
25	health economics/	34559
26	exp economic evaluation/	337213
27	exp health care cost/	322230
28	exp fee/	42496
29	budget/	32003
30	funding/	67739
31	budget*.ti,ab.	44183
32	cost*.ti.	181970
33	(economic* or pharmaco?economic*).ti.	70774
34	(price* or pricing*).ti,ab.	67140
35	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	264737
36	(financ* or fee or fees).ti,ab.	200470
37	(value adj2 (money or monetary)).ti,ab.	3792
38	or/25-37	1085390
39	statistical model/	171255
40	exp economic aspect/	2251504
41	39 and 40	27469
42	*theoretical model/	30994
43	*nonbiological model/	5065
44	stochastic model/	19388
45	decision theory/	1802
46	decision tree/	18095
47	monte carlo method/	46995
48	(markov* or monte carlo).ti,ab.	87061

#	Searches	
49	econom* model*.ti,ab.	7134
50	(decision* adj2 (tree* or analy* or model*)).ti,ab.	43807
51	or/41-50	225433
52	38 or 51	1266430
53	24 and 52	2248

Database: Cochrane Database of Systematic Reviews (CDSR) Issue 7 of 12, July 2022
Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	#7 and #37 with Cochrane Library publication date Between Jan 2012 and Aug 2022, in Cochrane Reviews	37

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7 of 12, July 2022
Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	"conference":pt or (clinicaltrials or trialsearch):so	608941
40	#38 not #39 with Publication Year from 2012 to 2022, in Trials	326

Database: EconLit <1886 to July 21, 2022>
Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	0
2	Menopause/ or Perimenopause/ or Postmenopause/ or exp Menopause Related Disorder/	0
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	70
4	("change of life" or life change?).tw.	92
5	or/1-4	162
6	limit 5 to yr="2012 -Current"	69

Database: CRD HTA

Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN HTA FROM 2012 TO 2022	42

Database: INAHTA

Date of last search: 28/07/2022

#	Searches	
1	"Climacteric"[mh]	2
2	"Menopause"[mh]	28
3	"Perimenopause"[mh]	1
4	"Postmenopause"[mh]	31
5	(menopau* or postmenopau* or perimenopau* or climacteri*)	159
6	("change of life" or "life change" or "life changes")	1
7	#6 OR #5 OR #4 OR #3 OR #2 OR #1	163
8	Limit to English Language	134

Database: EED

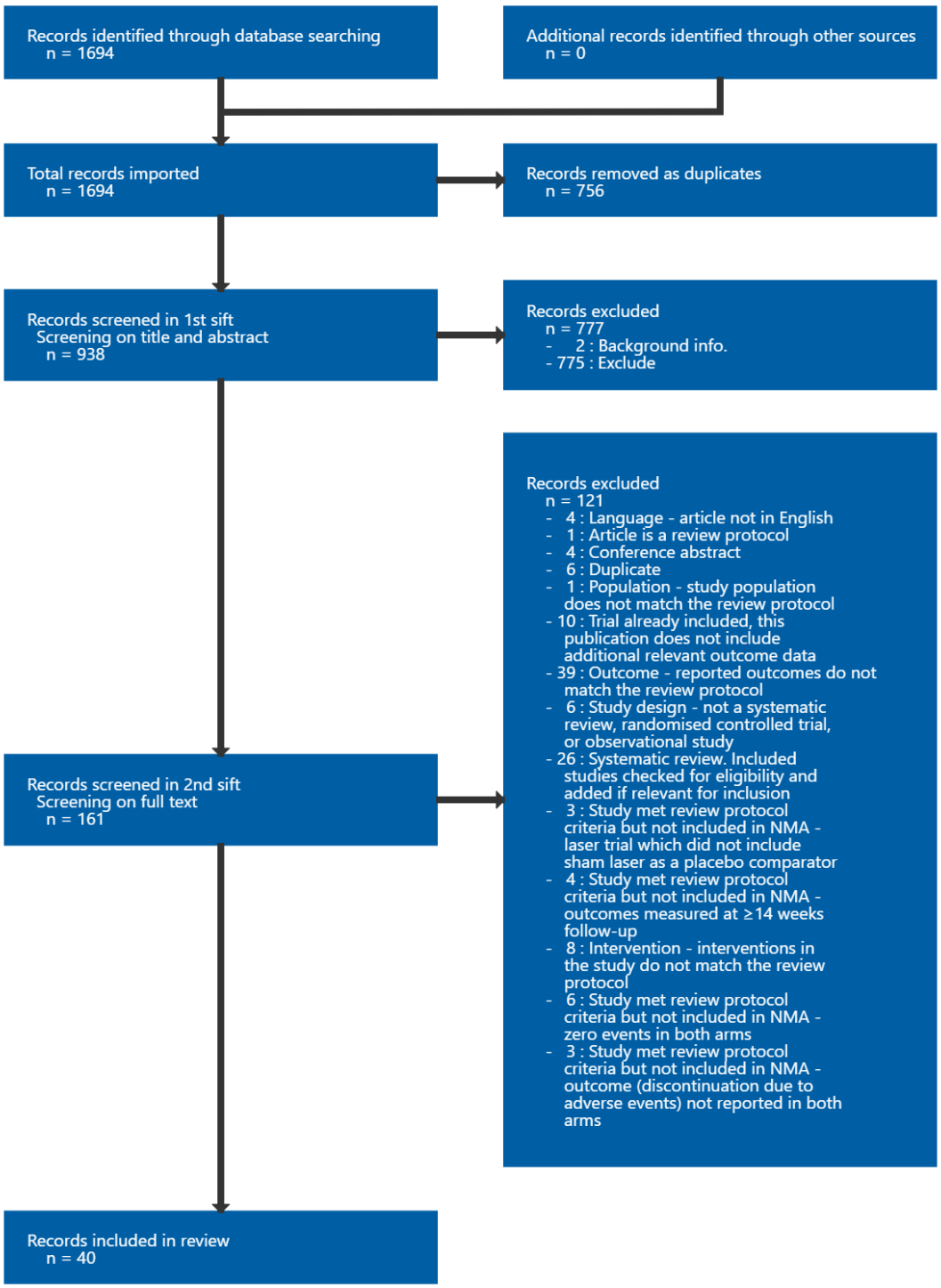
Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN NHSEED FROM 2012 TO 2022	33

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Figure 5: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Table 14: Evidence tables

Archer, 2015

Bibliographic Reference Archer, David F; Labrie, Fernand; Bouchard, Céline; Portman, David J; Koltun, William; Cusan, Leonello; Labrie, Claude; Côté, Isabelle; Lavoie, Lyne; Martel, Céline; Balser, John; Group, V V A Prasterone; Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone); Menopause; 2015; vol. 22 (no. 9); 950-963

Study details

Country/ies where study was carried out	US/Canada
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe pain at sexual activity (at screening and on day 1) Scale used to assess GU symptom severity for trial entry: Self-assessment (questionnaire) Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: PRASTERONE_LOW_DOSE** Age at study entry, mean (SD) years: 59.37 (NR) Age at study entry, median (range) years: 60 (40-75) Age at menopause, mean years: 43.91 Time since menopause at study entry, mean years: 15.47 **Arm 2: PRASTERONE** Age at study entry, mean (SD) years: 57.51 (NR) Age at study entry, median (range) years: 57 (41-69) Age at menopause, mean years: 43.48 Time since menopause at study entry, mean years: 14.02 **Arm 3: PLC_PESSARY**

	Age at study entry, mean (SD) years: 58.81 (NR) Age at study entry, median (range) years: 59 (45-73) Age at menopause, mean years: 44.94 Time since menopause at study entry, mean years: 13.88
Intervention(s)/control	**Arm 1: PRASTERONE_LOW_DOSE** 0.25% (3.25mg) DHEA suppository- daily administration **Arm 2: PRASTERONE** 0.50% (6.5mg) DHEA suppository- daily administration **Arm 3: PLC_PESSARY** Placebo pessary Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 255 N completers: 222 Analysis method: ITT ITT imputation method: LOCF
Outcome data	**Arm 1: PRASTERONE_LOW_DOSE** N randomised: 87 N completers: 74 discontinuation due to adverse events: 4 discontinuation for any reason: 13 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.56 dyspareunia baseline SD: 0.49 dyspareunia endpoint mean: 1.54 dyspareunia endpoint SD: 1.07 dyspareunia change from baseline mean: -1.02 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.2

	dryness baseline SD: 0.42 dryness endpoint mean: 0.91 dryness endpoint SD: 0.84 dryness change from baseline mean: -1.29 **Arm 2: PRASTERONE** N randomised: 87 N completers: 76 discontinuation due to adverse events: 2 discontinuation for any reason: 11 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.63 dyspareunia baseline SD: 0.45 dyspareunia endpoint mean: 1.36 dyspareunia endpoint SD: 1.08 dyspareunia change from baseline mean: -1.27 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.37 dryness baseline SD: 0.47 dryness endpoint mean: 0.92 dryness endpoint SD: 0.79 dryness change from baseline mean: -1.45 **Arm 3: PLC_PESSARY** N randomised: 81 N completers: 72 discontinuation due to adverse events: 1 discontinuation for any reason: 9 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.58 dyspareunia baseline SD: 0.53 dyspareunia endpoint mean: 1.71 dyspareunia endpoint SD: 0.97 dyspareunia change from baseline mean: -0.87 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.33 dryness baseline SD: 0.46 dryness endpoint mean: 1.32

	dryness endpoint SD: 0.93 dryness change from baseline mean: -1.01

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation sequence was random and concealed with no baseline differences between intervention groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded and ITT analysis used)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(More than 5% withdrawals- balanced between arms)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns *(Outcome is self-reported)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All the outcomes listed in the registered protocol were all reported)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in two domains due to insufficient information)*
Overall bias and directness	Overall directness	Directly applicable

2 **Archer, 2018**

Bibliographic Archer, David F; Kimble, Thomas D; Lin, F D Yuhua; Battucci, Simona; Sniukiene, Vilma; Liu, James H; A randomized,

Reference multicenter, double-blind, study to evaluate the safety and efficacy of estradiol vaginal cream 0.003% in postmenopausal women with vaginal dryness as the most bothersome symptom; J. Womens. Health (Larchmt); 2018; vol. 27 (no. 3); 231-237

1 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vaginal dryness (as most bothersome GU symptom) Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: ESTRADIOL_CREAM** Age at study entry, mean (SD) years: 59.5 (6.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: PLC_TOPICAL** Age at study entry, mean (SD) years: 59.8 (6.1) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRADIOL_CREAM** estradiol vaginal cream 0.003% (0.5 g of cream daily for 2 weeks then 2 times per week) **Arm 2: PLC_TOPICAL** 0.5g placebo cream Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded

Sample size	N randomised: 576 N completers: 526 Analysis method: mITT ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_CREAM** N randomised: 287 N completers: 265 discontinuation due to adverse events: 8 discontinuation for any reason: 22 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.1 dyspareunia baseline SD: 1 dyspareunia endpoint mean: 1.11 dyspareunia endpoint SD: -0.99 dyspareunia change from baseline mean: 1.11 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.5 dryness baseline SD: 0.5 dryness endpoint mean: 1.3 dryness endpoint SD: -1.2 dryness change from baseline mean: 0.9 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 1.1 discomfort baseline SD: 1 discomfort endpoint mean: 0.5 discomfort endpoint SD: -0.6 discomfort change from baseline mean: 0.98 dysuria scale used: 4-point scale (0-3;LB) dysuria baseline mean: 0.4 dysuria baseline SD: 0.7 **Arm 2: PLC_TOPICAL** N randomised: 289 N completers: 261 discontinuation due to adverse events: 6 discontinuation for any reason: 28

	dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.1 dyspareunia baseline SD: 0.9 dyspareunia endpoint mean: 1.1 dyspareunia endpoint SD: -1 dyspareunia change from baseline mean: 0.95 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.5 dryness baseline SD: 0.5 dryness endpoint mean: 1.1 dryness endpoint SD: -1.4 dryness change from baseline mean: 0.9 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 1.1 discomfort baseline SD: 1 discomfort endpoint mean: 0.41 discomfort endpoint SD: -0.69 discomfort change from baseline mean: 0.99 dysuria scale used: 4-point scale (0-3;LB) dysuria baseline mean: 0.3 dysuria baseline SD: 0.7

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on concealment process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Study was double blinded with no deviations,)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome	Some concerns *(Data only available from 85% participants.)*

	data	
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(No information on blinding of assessors however knowledge of assignment unlikely to influence outcome results.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Trial protocol not available.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in three domains due to insufficient information and data)*
Overall bias and directness	Overall directness	Directly applicable

1 **Archer, 2019**

Bibliographic Reference Archer, David F; Goldstein, Steven R; Simon, James A; Waldbaum, Arthur S; Sussman, Steven A; Altomare, Corrado; Zhu, Julie; Yoshida, Yuki; Schaffer, Sam; Soulban, Graziella; Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: a phase 3, randomized, double-blind, placebo-controlled, multicenter trial.; Menopause (New York, N.Y.); 2019; vol. 26 (no. 6); 611-621

2 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vaginal dryness (as most bothersome GU symptom) Scale used to assess GU symptom severity for trial entry: Self-assessment (questionnaire) Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: OSPEMIFENE** Age at study entry, mean (SD) years: 59.7 (6.6) Age at study entry, median (range) years: NR(NR-NR)

	Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: PLC_ORAL** Age at study entry, mean (SD) years: 59.8 (7.2) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: OSPEMIFENE** Ospemifene 60mg oral tablet; 1 per day for 12 weeks **Arm 2: PLC_ORAL** placebo oral tablet Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 627 N completers: 558 Analysis method: ITT ITT imputation method: mixed-effects model for repeated measures (no LOCF)
Outcome data	**Arm 1: OSPEMIFENE** N randomised: 313 N completers: 280 discontinuation due to adverse events: 6 discontinuation for any reason: 33 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.5 dyspareunia baseline SD: 0.5 dyspareunia endpoint mean: 0.9 dyspareunia endpoint SD: -1.6 dyspareunia change from baseline mean: 1 dryness scale used: 4-point scale (0-3;LB)

	dryness baseline mean: 2.53 dryness baseline SD: 0.5 dryness endpoint mean: 1.24 dryness endpoint SD: -1.29 dryness change from baseline mean: 1.01 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 2.3 discomfort baseline SD: 0.4 discomfort endpoint mean: 0.7 discomfort endpoint SD: -1.6 discomfort change from baseline mean: 0.8 **Arm 2: PLC_ORAL** N randomised: 314 N completers: 278 discontinuation due to adverse events: 10 discontinuation for any reason: 36 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.5 dyspareunia baseline SD: 0.5 dyspareunia endpoint mean: 1.3 dyspareunia endpoint SD: -1.2 dyspareunia change from baseline mean: 1.1 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.54 dryness baseline SD: 0.5 dryness endpoint mean: 1.63 dryness endpoint SD: -0.91 dryness change from baseline mean: 0.96 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 2.3 discomfort baseline SD: 0.4 discomfort endpoint mean: 0.7 discomfort endpoint SD: -1.6 discomfort change from baseline mean: 1.1000000000000001

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation sequence was random and concealed with no baseline differences between intervention groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and staff were unaware of participants' assignments. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for nearly all participants randomised.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measure used.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Analysis plan not specified in registered protocol.)*
Overall bias and directness	Risk of bias judgement	Low *(All domains except domain 5 are of low concern. Domain 5 had some concerns due to missing information in the trial protocol.)*
Overall bias and directness	Overall directness	Directly applicable

2 **Ayton, 1996**

Bibliographic Reference Ayton, R A; Darling, G M; Murkies, A L; Farrell, E A; Weisberg, E; Selinus, I; Fraser, I D; A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy; British journal of obstetrics and gynaecology; 1996; vol. 103 (no. 4ccgynaecologyandfertilitycckidneyandtransplant); 351-358

1 **Study details**

Country/ies where study was carried out	Australia
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Any symptoms of vaginal dryness with or without dyspareunia pruritus, dysuria and/or urgency, and signs of atrophic vaginitis. Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_RING** Age at study entry, mean (SD) years: 59.3 (7.3) Age at study entry, median (range) years: NR(36-86) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 9.4 **Arm 2: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 59.9 (7.3) Age at study entry, median (range) years: NR(46-82) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 9.2
Intervention(s)/control	**Arm 1: ESTRADIOL_RING** Low dose estradiol vaginal ring (Estring) **Arm 2: CONJ_ESTROGEN_CREAM** Conjugated equine oestrogen vaginal cream (Premarin). 1 g of cream (0.625 mg equine estrogens) every night for three weeks followed by one week free of treatment. Then cycle repeated. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded

Sample size	N randomised: 194 N completers: 176 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_RING** N randomised: 131 N completers: 120 discontinuation due to adverse events: 9 discontinuation for any reason: 11 **Arm 2: CONJ_ESTROGEN_CREAM** N randomised: 63 N completers: 56 discontinuation due to adverse events: 5 discontinuation for any reason: 7

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Random number computer generating programme used for randomisation. Allocation was concealed and no differences at baselines between the groups.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Unclear if people delivering the interventions were blinded of participants' assignments during the trial)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Nearly all outcome data reported)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used and assessors were blinded to intervention received.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Insufficient information provided and no protocol available.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study rated with some concerns in 2 domains due to insufficient information.)*
Overall bias and directness	Overall directness	Directly applicable

1 **Bachmann, 1997**

Bibliographic Reference Bachmann, G; Notelovitz, M; Nachtigall, L; Birgerson, L; A comparative study of a low-dose estradiol vaginal ring and conjugated estrogen cream for postmenopausal urogenital atrophy; Primary care update for Ob/Gyns; 1997; vol. 4 (no. 3ccgynaecologyandfertility); 109-115

2 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Symptoms of vaginal dryness and one or more signs of vaginal atrophy Scale used to assess GU symptom severity for trial entry: Clinical diagnosis Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: ESTRADIOL_RING** Age at study entry, mean (SD) years: 56.6 (NR) Age at study entry, median (range) years: NR(35-76) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 10.2 **Arm 2: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 57.3 (NR)

	Age at study entry, median (range) years: NR(36-74) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 10.6
Intervention(s)/control	**Arm 1: ESTRADIOL_RING** Low dose estradiol vaginal ring (Estring) **Arm 2: CONJ_ESTROGEN_CREAM** Conjugated equine oestrogen vaginal cream (Premarin). 2 g of cream (1.250 mg equine estrogens) 3 times per week. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 196 N completers: 173 Analysis method: ITT ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_RING** N randomised: 129 N completers: 113 discontinuation due to adverse events: 5 discontinuation for any reason: 16 **Arm 2: CONJ_ESTROGEN_CREAM** N randomised: 67 N completers: 60 discontinuation due to adverse events: 0 discontinuation for any reason: 7

1 **Critical appraisal**

Section	Question	Answer

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no difference at baseline between groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Open label study with appropriate analysis but no information on deviations.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Most outcome data available)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Assessors were blinded to appropriate outcome measured.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in two domains)*
Overall bias and directness	Overall directness	Directly applicable

1 **Bachmann, 2008**

Bibliographic Reference Bachmann, G; Lobo, R A; Gut, R; Nachtigall, L; Notelovitz, M; Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial; Obstetrics and gynecology; 2008; vol. 111 (no. 1ccgynaecologyandfertility); 67-76

2 **Study details**

Country/ies where study was carried out	United States

Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vaginal dryness and soreness. Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_TAB** Age at study entry, mean (SD) years: 57.7 (6.5) Age at study entry, median (range) years: NR(46-79) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 13.5 **Arm 2: ESTRADIOL_TAB** Age at study entry, mean (SD) years: 58.3 (7.4) Age at study entry, median (range) years: NR(46-78) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 14.8 **Arm 3: PLC_PESSARY** Age at study entry, mean (SD) years: 57.6 (4.8) Age at study entry, median (range) years: NR(50-70) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 13.6
Intervention(s)/control	**Arm 1: ESTRADIOL_TAB** 10µg estradiol vaginal tablet. Once daily for 2 weeks then twice-weekly for 10 weeks. **Arm 2: ESTRADIOL_TAB** 25µg estradiol vaginal tablet. Once daily for 2 weeks then twice-weekly for 10 weeks. **Arm 3: PLC_PESSARY** Placebo vaginal tablet. Once daily for 2 weeks then twice-weekly for 10 weeks. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded

Sample size	N randomised: 230 N completers: 195 Analysis method: ITT ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_TAB** N randomised: 92 N completers: 74 discontinuation due to adverse events: 6 discontinuation for any reason: 18 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 1.83 discomfort baseline SD: 0.54 discomfort endpoint mean: 0.58 discomfort endpoint SD: 0.77 discomfort change from baseline mean: -1.26 **Arm 2: ESTRADIOL_TAB** N randomised: 91 N completers: 82 discontinuation due to adverse events: 4 discontinuation for any reason: 9 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 1.86 discomfort baseline SD: 0.6 discomfort endpoint mean: 0.44 discomfort endpoint SD: 0.49 discomfort change from baseline mean: -1.41 **Arm 3: PLC_PESSARY** N randomised: 47 N completers: 39 discontinuation due to adverse events: 1 discontinuation for any reason: 8 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 1.94 discomfort baseline SD: 0.66 discomfort endpoint mean: 1.08

	discomfort endpoint SD: 1.09 discomfort change from baseline mean: -0.87

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation process with no differences at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded trial with ITT analysis.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Only 70-80% of outcome data available; however ITT analysis used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures used with assessors blinded to type of intervention received.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data reported analysed as specified in methodology.)*
Overall bias and directness	Risk of bias judgement	Low *(Study was rated as low concern in all domains)*
Overall bias and directness	Overall directness	Directly applicable

2 **Bachmann, 2009**

Bibliographic Reference Bachmann, Gloria; Bouchard, Céline; Hoppe, Diana; Ranganath, Radhika; Altomare, Corrado; Vieweg, Alberta; Graepel, Jay; Helzner, Eileen; Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally; Menopause;

2009; vol. 16 (no. 4); 719-727

1 **Study details**

Country/ies where study was carried out	US/Canada
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vaginal dryness, itching, and burning or dyspareunia. Scale used to assess GU symptom severity for trial entry: Self reported (4-point scale) Uterus or not: Uterus Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 57.7 (5.8) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 8.9 **Arm 2: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 57.5 (5.5) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 7.9 **Arm 3: PLC_TOPICAL** Age at study entry, mean (SD) years: 58 (5.8) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 9.7 **Arm 4: PLC_TOPICAL** Age at study entry, mean (SD) years: 58.7 (5.8) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 9.9
Intervention(s)/control	**Arm 1: CONJ_ESTROGEN_CREAM** Conjugated equine oestrogen vaginal cream (Premarin). 0.5 g of cream (0.3 mg equine estrogens) every night for three

	weeks followed by one week free of treatment. Then cycle repeated. **Arm 2: CONJ_ESTROGEN_CREAM** Conjugated equine oestrogen vaginal cream (Premarin). 0.5 g of cream (0.3 mg equine estrogens) twice weekly. **Arm 3: PLC_TOPICAL** Placebo vaginal cream. 0.5 g of cream every night for three weeks followed by one week free of treatment. Then cycle repeated. **Arm 4: PLC_TOPICAL** Placebo vaginal cream 0.5 g of cream twice weekly. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 423 N completers: 394 Analysis method: mITT ITT imputation method: NR
Outcome data	**Arm 1: CONJ_ESTROGEN_CREAM** N randomised: 143 N completers: 129 discontinuation due to adverse events: 6 discontinuation for any reason: 14 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.2 dyspareunia baseline SD: 0.8 dyspareunia endpoint mean: -1.4 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.6 dryness baseline SD: 0.5 dryness endpoint mean: -1.1 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 0.6 discomfort baseline SD: 0.4

	discomfort endpoint mean: -0.2 **Arm 2: CONJ_ESTROGEN_CREAM** N randomised: 140 N completers: 132 discontinuation due to adverse events: 4 discontinuation for any reason: 8 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.1 dyspareunia baseline SD: 0.7 dyspareunia endpoint mean: -1.4 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.8 dryness baseline SD: 0.7 dryness endpoint mean: -1.1 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 0.7 discomfort baseline SD: 0.4 discomfort endpoint mean: -0.3 **Arm 3: PLC_TOPICAL** N randomised: 72 N completers: 69 discontinuation due to adverse events: 1 discontinuation for any reason: 3 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.2 dyspareunia baseline SD: 1.8 dyspareunia endpoint mean: -0.4 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.8 dryness baseline SD: 1.1 dryness endpoint mean: -0.7 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 0.9 discomfort baseline SD: 0.4 discomfort endpoint mean: -0.5 **Arm 4: PLC_TOPICAL**

	N randomised: 68 N completers: 64 discontinuation due to adverse events: 2 discontinuation for any reason: 4 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.1 dyspareunia baseline SD: 1.4 dyspareunia endpoint mean: -0.7 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.8 dryness baseline SD: 1 dryness endpoint mean: -0.8 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 0.8 discomfort baseline SD: 0.6 discomfort endpoint mean: -0.2

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on concealment provided)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded trial with modified ITT analysis.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Nearly all outcome data reported (at least 90%))*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures used)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data reported and analysed according to methodology)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study showed some concerns in one domain due to insufficient information)*
Overall bias and directness	Overall directness	Directly applicable

1 **Bachmann, 2010**

Bibliographic Reference Bachmann, Gloria A; Komi, Janne O; Group, Ospemifene Study; Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study; Menopause; 2010; vol. 17 (no. 3); 480-486

2 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vulvovaginal atrophy Scale used to assess GU symptom severity for trial entry: FDA guidelines for drug development (2003) Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: OSPEMIFENE** Age at study entry, mean (SD) years: 58.6 (6.3) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 14.6 **Arm 2: OSPEMIFENE_LOW_DOSE** Age at study entry, mean (SD) years: 58.4 (6.3) Age at study entry, median (range) years: NR(NR-NR)

	Age at menopause, mean years: NR Time since menopause at study entry, mean years: 14.4 **Arm 3: PLC_ORAL** Age at study entry, mean (SD) years: 58.9 (6.1) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 15.4
Intervention(s)/control	**Arm 1: OSPEMIFENE** 60mg Ospemifene oral tablet daily. **Arm 2: OSPEMIFENE_LOW_DOSE** 30mg Ospemifene oral tablet daily. **Arm 3: PLC_ORAL** Placebo oral tablet daily. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 826 N completers: 689 Analysis method: ITT ITT imputation method: LOCF
Outcome data	**Arm 1: OSPEMIFENE** N randomised: 276 N completers: 234 discontinuation due to adverse events: 13 discontinuation for any reason: 42 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.6 dyspareunia baseline SD: 0.7 dyspareunia endpoint mean: -1.19 dryness scale used: 4-point scale (0-3;LB)

	dryness baseline mean: 2.4 dryness baseline SD: 0.6 dryness endpoint mean: -1.26 **Arm 2: OSPEMIFENE_LOW_DOSE** N randomised: 282 N completers: 225 discontinuation due to adverse events: 15 discontinuation for any reason: 57 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.6 dyspareunia baseline SD: 0.7 dyspareunia endpoint mean: -1.02 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.5 dryness baseline SD: 0.6 dryness endpoint mean: -1.22 **Arm 3: PLC_ORAL** N randomised: 268 N completers: 230 discontinuation due to adverse events: 13 discontinuation for any reason: 38 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.7 dyspareunia baseline SD: 0.6 dyspareunia endpoint mean: -0.89 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.4 dryness baseline SD: 0.5 dryness endpoint mean: -0.84

1

2 **Critical appraisal**

Section	Question	Answer

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Concealment method not described)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with ITT)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used with assessors unaware of intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Trial protocol unavailable.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in two domains.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Barentsen, 1997**

Bibliographic Reference Barentsen, R; van de Weijer, P H; Schram, J H; Continuous low dose estradiol released from a vaginal ring versus estriol vaginal cream for urogenital atrophy; European journal of obstetrics, gynecology, and reproductive biology; 1997; vol. 71 (no. 1ccgynaecologyandfertility); 73-80

3 **Study details**

Country/ies where	Netherlands

study was carried out	
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Any signs or symptoms of vaginal atrophy Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: ESTRADIOL_RING** Age at study entry, mean (SD) years: 57.9 (NR) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 8.5 **Arm 2: ESTRIOL_CREAM** Age at study entry, mean (SD) years: 58.5 (NR) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 9.4
Intervention(s)/control	**Arm 1: ESTRADIOL_RING** Estradiol vaginal ring (Estring) with a constant release of around 7.5 Âµg estradiol/24 h for 90 days. **Arm 2: ESTRIOL_CREAM** Vaginal estriol cream (Synapause). 1 mg estriol/g of cream. s 0.5 mg daily for the first 2 weeks then 0.5 mg three times weekly. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 165 N completers: 138 Analysis method: ITT ITT imputation method: NR

Outcome data	**Arm 1: ESTRADIOL_RING** N randomised: 83 N completers: 72 discontinuation due to adverse events: 2 discontinuation for any reason: 11 **Arm 2: ESTRIOL_CREAM** N randomised: 82 N completers: 66 discontinuation due to adverse events: 3 discontinuation for any reason: 16

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on concealment provided)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Insufficient information on if people delivering the interventions were blinded and on deviations from intended intervention)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available in ITT analysis for all patients who started treatment)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Unclear if assessors were aware of intervention received; however appropriate measures were used.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Insufficient information in methodology provided.)*
Overall bias and directness	Risk of bias judgement	High

Section	Question	Answer
		(Several domains were rated with some concerns.)
Overall bias and directness	Overall directness	Directly applicable

1

2 **Barton, 2018**

Bibliographic Reference Barton, Debra L; Sloan, Jeff A; Shuster, Lynne T; Gill, Paula; Griffin, Patricia; Flynn, Kathleen; Terstriep, Shelby A; Rana, Fauzia N; Dockter, Travis; Atherton, Pamela J; Tsai, Michaela; Sturtz, Keren; Lafky, Jacqueline M; Riepl, Mike; Thielen, Jacqueline; Loprinzi, Charles L; Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance); Support. Care Cancer; 2018; vol. 26 (no. 2); 643-650

3 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vaginal dryness or dyspareunia Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus Breast or gynae cancer history: Breast or gynae cancer
Patient characteristics	**Arm 1: PRASTERONE_LOW_DOSE** Age at study entry, mean (SD) years: 56.8 (6.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: PRASTERONE** Age at study entry, mean (SD) years: 57.3 (8.2) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR

	Time since menopause at study entry, mean years: NR **Arm 3: MOISTURISER** Age at study entry, mean (SD) years: 58 (7.3) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: PRASTERONE_LOW_DOSE** 0.25% (3.25mg) DHEA in moisturiser gel - via syringe applicator. Daily for 12 weeks **Arm 2: PRASTERONE** 0.50% (6.5mg) DHEA in moisturiser gel - via syringe applicator. Daily for 12 weeks **Arm 3: MOISTURISER** moisturiser gel- via syringe applicator. Daily for 12 weeks Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms
Duration of follow-up	12 weeks
Sources of funding	Not industry funded
Sample size	N randomised: 443 N completers: 355 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: PRASTERONE_LOW_DOSE** N randomised: 147 N completers: 123 discontinuation due to adverse events: 13 discontinuation for any reason: 24 dyspareunia scale used: 5-point scale (1-5;LB) dyspareunia baseline mean: -1.3 dyspareunia baseline SD: 1.23 dryness scale used: 5-point scale (1-5;LB) dryness baseline mean: -1.3 dryness baseline SD: 1.46

	Arm 2: PRASTERONE N randomised: 149 N completers: 114 discontinuation due to adverse events: 17 discontinuation for any reason: 35 dyspareunia scale used: 5-point scale (1-5;LB) dyspareunia baseline mean: -1.5 dyspareunia baseline SD: 1.5 dryness scale used: 5-point scale (1-5;LB) dryness baseline mean: -1.5 dryness baseline SD: 1.07 **Arm 3: MOISTURISER** N randomised: 147 N completers: 118 discontinuation due to adverse events: 14 discontinuation for any reason: 29 dyspareunia scale used: 5-point scale (1-5; LB) dyspareunia baseline mean: -1.4 dyspareunia baseline SD: 1.15 dryness scale used: 5-point scale (1-5; LB) dryness baseline mean: -1.4 dryness baseline SD: 1.1

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was concealed with no differences at baseline)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Double blinded study with outcome unaffected.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome	High concerns *(Data available only for 80% of participants. No large*

Section	Question	Answer
	data	*drop out rates differences between the groups. Completer analysis was used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Outcomes were self-rated scales however participants were unaware of assignment of intervention.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available)*
Overall bias and directness	Risk of bias judgement	High risk of bias *(Study had some concerns in one domain and high risk of bias due to missing data.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Bosak, 2019**

Bibliographic Reference Bosak, Z; Iravani, M; Moghimipour, E; Haghighizadeh, MH; Jelodarian, P; Evaluation of the effect of chamomile vaginal gel on subjective symptoms of vaginal atrophy in postmenopausal women: a randomized clinical controlled trial; Iranian journal of obstetrics, gynecology and infertility; 2019; vol. 22 (no. 7); 23-31

3 **Study details**

Country/ies where study was carried out	Iran, Islamic Republic of
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: vaginal atrophy symptoms and dyspareunia Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus

	Breast or gynae cancer history: None
Patient characteristics	**Arm 1: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 53.8 (3.2) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 49.3 Time since menopause at study entry, mean years: NR **Arm 2: PLC_TOPICAL** Age at study entry, mean (SD) years: 53.7 (2) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 49.5 Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: CONJ_ESTROGEN_CREAM** Conjugated estrogen cream (daily for 2 weeks then 2 times per week for the next 10 weeks) **Arm 2: PLC_TOPICAL** Placebo gel (daily for 2 weeks then 2 times per week for the next 10 weeks) Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No
Duration of follow-up	12 weeks
Sources of funding	Not reported
Sample size	N randomised: 64 N completers: 59 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: CONJ_ESTROGEN_CREAM** N randomised: 32 N completers: 32 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: 4-point scale (0-3;LB)

	dyspareunia baseline mean: 2.16 dyspareunia baseline SD: 0.68 dyspareunia endpoint mean: 0.03 dyspareunia endpoint SD: 0.18 dyspareunia change from baseline mean: -2.13 **Arm 2: PLC_TOPICAL** N randomised: 32 N completers: 27 discontinuation due to adverse events: 1 discontinuation for any reason: 5 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.15 dyspareunia baseline SD: 0.66 dyspareunia endpoint mean: 1.89 dyspareunia endpoint SD: 0.7 dyspareunia change from baseline mean: -0.26

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Concealment method not described.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with outcomes unaffected.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(Data available for at least 85% with difference between groups. Drop outs were higher in placebo group due to unwillingness to continue.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Outcomes were self rated scales by blinded participants.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High *(Only 2 out of 5 trial outcomes were reported.)*
Overall bias and directness	Risk of bias judgement	High *(Study had high risk of bias in selecting of reporting results.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Bouchard, 2015**

Bibliographic Reference Bouchard, C; Labrie, F; Archer, D F; Portman, D J; Koltun, W; Elfassi, É; Grainger, D A; Ayotte, N; Cooper, T A; Martens, M; Waldbaum, A S; Labrie, C; Côté, I; Lavoie, L; Martel, C; Balser, J; Group, V V A Prasterone; Decreased efficacy of twice-weekly intravaginal dehydroepiandrosterone on vulvovaginal atrophy; Climacteric; 2015; vol. 18 (no. 4); 590-607

3 **Study details**

Country/ies where study was carried out	US/Canada
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vaginal dryness as the most bothersome vaginal atrophy symptom Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: PRASTERONE** Age at study entry, mean (SD) years: 58.33 (NR) Age at study entry, median (range) years: 58 (43-74) Age at menopause, mean years: 45.55 Time since menopause at study entry, mean years: 12.78

	Arm 2: PRASTERONE_LOW_DOSE Age at study entry, mean (SD) years: 58.41 (NR) Age at study entry, median (range) years: 58 (44-75) Age at menopause, mean years: 45.89 Time since menopause at study entry, mean years: 12.52 **Arm 3: PLC_PESSARY** Age at study entry, mean (SD) years: 57.59 (NR) Age at study entry, median (range) years: 57 (41-75) Age at menopause, mean years: 44.89 Time since menopause at study entry, mean years: 12.7
Intervention(s)/control	**Arm 1: PRASTERONE** 0.50% (6.5mg) DHEA suppository- daily administration for 2 weeks, then 2x/week for 10 weeks **Arm 2: PRASTERONE_LOW_DOSE** 0.25% (3.25mg) DHEA suppository- daily administration for 2 weeks, then 2x/week for 10 weeks **Arm 3: PLC_PESSARY** Placebo pessary- daily administration for 2 weeks, then 2x/week for 10 weeks Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 450 N completers: 383 Analysis method: ITT ITT imputation method: LOCF
Outcome data	**Arm 1: PRASTERONE** N randomised: 150 N completers: 125 discontinuation due to adverse events: 3 discontinuation for any reason: 25 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.6

	dyspareunia baseline SD: 0.61 dyspareunia endpoint mean: 1.54 dyspareunia endpoint SD: 1.22 dyspareunia change from baseline mean: -1.06 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.35 dryness baseline SD: 0.49 dryness endpoint mean: 1.13 dryness endpoint SD: 0.98 dryness change from baseline mean: -1.22 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 2.25 discomfort baseline SD: 0.61 discomfort endpoint mean: 0.84 discomfort endpoint SD: 1.22 discomfort change from baseline mean: -1.41 **Arm 2: PRASTERONE_LOW_DOSE** N randomised: 148 N completers: 128 discontinuation due to adverse events: 4 discontinuation for any reason: 20 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.58 dyspareunia baseline SD: 0.61 dyspareunia endpoint mean: 1.48 dyspareunia endpoint SD: 1.46 dyspareunia change from baseline mean: -1.1 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.37 dryness baseline SD: 0.49 dryness endpoint mean: 1.1 dryness endpoint SD: 0.85 dryness change from baseline mean: -1.27 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 2.28 discomfort baseline SD: 0.73

	discomfort endpoint mean: 0.67 discomfort endpoint SD: 1.22 discomfort change from baseline mean: -1.61 **Arm 3: PLC_PESSARY** N randomised: 152 N completers: 130 discontinuation due to adverse events: 3 discontinuation for any reason: 22 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.56 dyspareunia baseline SD: 0.62 dyspareunia endpoint mean: 1.78 dyspareunia endpoint SD: 1.36 dyspareunia change from baseline mean: -0.78 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.38 dryness baseline SD: 0.49 dryness endpoint mean: 1.27 dryness endpoint SD: 0.86 dryness change from baseline mean: -1.11 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 2.26 discomfort baseline SD: 0.62 discomfort endpoint mean: 1.09 discomfort endpoint SD: 1.36 discomfort change from baseline mean: -1.17

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended	Low *(Study was double blinded and ITT analysis*

Section	Question	Answer
intended interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	*used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Outcome data available only for at least 85% participants however ITT analysis used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used with assessors blinded to intervention.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All outcome measures and analysis as per trial protocol reported.)*
Overall bias and directness	Risk of bias judgement	Low *(Study had low risk of bias for all concerns.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Bumphenkiatikul, 2020**

Bibliographic Reference Bumphenkiatikul, Thanapob; Panyakhamlerd, Krasean; Chatsuwan, Thanittha; Ariyasriwatana, Chai; Suwan, Ammarin; Taweepolcharoen, Charoen; Taechakraichana, Nimit; Effects of vaginal administration of conjugated estrogens tablet on sexual function in postmenopausal women with sexual dysfunction: a double-blind, randomized, placebo-controlled trial.; BMC women's health; 2020; vol. 20 (no. 1); 173

3 **Study details**

Country/ies where study was carried out	Thailand
Study type	Randomised controlled trial (RCT)

Inclusion / exclusion criteria	GU symptom inclusion criteria: moderate to severe vaginal atrophy symptoms Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: CONJ_ESTROGEN_TAB** Age at study entry, mean (SD) years: 57.41 (4.85) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 50.74 Time since menopause at study entry, mean years: 6.68 **Arm 2: PLC_PESSARY** Age at study entry, mean (SD) years: 57.03 (4.65) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 50.3 Time since menopause at study entry, mean years: 6.73
Intervention(s)/control	**Arm 1: CONJ_ESTROGEN_TAB** Conjugated estrogen 0.625mg vaginal tablet (daily for 3 weeks then 2 times per week for the next 9 weeks) **Arm 2: PLC_PESSARY** Placebo vaginal tablet (daily for 3 weeks then 2 times per week for the next 9 weeks) Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Not industry funded
Sample size	N randomised: 67 N completers: 58 Analysis method: ITT ITT imputation method: multiple imputation
Outcome data	**Arm 1: CONJ_ESTROGEN_TAB** N randomised: 34 N completers: 29 discontinuation due to adverse events: 1

	discontinuation for any reason: 5 dyspareunia scale used: tFSFI - transformed FSFI pain domain (0-6;LB) dyspareunia baseline mean: 2.29 dyspareunia baseline SD: 1.87 dyspareunia endpoint mean: 0.87 dyspareunia endpoint SD: 0.95 dyspareunia change from baseline mean: -1.42 dryness scale used: tFSFI - transformed FSFI lubrication domain (0-6;LB) dryness baseline mean: 2.54 dryness baseline SD: 1.27 dryness endpoint mean: 1.46 dryness endpoint SD: 1.16 dryness change from baseline mean: -1.08 discomfort scale used: 4-point scale (0-3;LB) **Arm 2: PLC_PESSARY** N randomised: 33 N completers: 29 discontinuation due to adverse events: 0 discontinuation for any reason: 4 dyspareunia scale used: tFSFI - transformed FSFI pain domain (0-6;LB) dyspareunia baseline mean: 2.1 dyspareunia baseline SD: 1.51 dyspareunia endpoint mean: 1.34 dyspareunia endpoint SD: 1.05 dyspareunia change from baseline mean: -0.76 dryness scale used: tFSFI - transformed FSFI lubrication domain (0-6;LB) dryness baseline mean: 2.02 dryness baseline SD: 1.04 dryness endpoint mean: 1.8 dryness endpoint SD: 1.03 dryness change from baseline mean: -0.22 discomfort scale used: 4-point scale (0-3;LB)

1 **Critical appraisal**

Section	Question	Answer

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was concealed with no differences at baseline between groups found)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded trial with ITT analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Drop out rate was at least 12% however ITT analysis was used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures were used with assessors including participants blinded to intervention.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All outcome data was recorded and analysed according to trial protocol.)*
Overall bias and directness	Risk of bias judgement	Low *(Study had low risk of bias in all domains.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Cagnacci, 2022**

Bibliographic Reference Cagnacci, Angelo; Barattini, Dionisio Franco; Casolati, Elena; Pecoroni, Alberto; Mangrella, Mario; Patrascu, Liviu Cristian; Polycarbophil vaginal moisturizing gel versus hyaluronic acid gel in women affected by vaginal dryness in late menopausal transition: A prospective randomized trial.; European journal of obstetrics, gynecology, and reproductive biology; 2022; vol. 270; 239-245

1 **Study details**

Country/ies where study was carried out	Romania
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Vulvovaginal atrophy Scale used to assess GU symptom severity for trial entry: Clinical diagnosis Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: MOISTURISER** Age at study entry, mean (SD) years: 48.76 (3.18) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: LUBRICANT** Age at study entry, mean (SD) years: 50.23 (2.52) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: MOISTURISER** Intravaginal polycarbophil moisturizer gel. 1 g of PCV gel (Ainara) twice a week for 30 days. **Arm 2: LUBRICANT** Intravaginal hyaluronic acid gel .3 g of gel (Hyalo Gyn) 3 times per week for 30 days. Treatment duration (weeks): 4.3 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol
Duration of follow-up	4.3 weeks
Sources of funding	Industry funded
Sample size	N randomised: 56 N completers: 53 Analysis method: completers

	ITT imputation method: NR
Outcome data	**Arm 1: MOISTURISER** N randomised: 29 N completers: 28 discontinuation due to adverse events: 0 discontinuation for any reason: 1 dyspareunia scale used: VAS scale (0-100;LB) dyspareunia baseline mean: 35.5 dyspareunia baseline SD: 20.41 dyspareunia endpoint mean: 8.36 dyspareunia endpoint SD: 10.03 dyspareunia change from baseline mean: -27.14 dryness scale used: VAS scale (0-100;LB) dryness baseline mean: 48.14 dryness baseline SD: 16.14 dryness endpoint mean: 14.93 dryness endpoint SD: 16.72 dryness change from baseline mean: -33.21 discomfort scale used: VAS scale (0-100;LB) discomfort baseline mean: 37.54 discomfort baseline SD: 20.03 discomfort endpoint mean: 8.86 discomfort endpoint SD: 10.77 discomfort change from baseline mean: -28.68 **Arm 2: LUBRICANT** N randomised: 27 N completers: 25 discontinuation due to adverse events: 0 discontinuation for any reason: 2 dyspareunia scale used: VAS scale (0-100;LB) dyspareunia baseline mean: 34 dyspareunia baseline SD: 18.25 dyspareunia endpoint mean: 9.68 dyspareunia endpoint SD: 10.38 dyspareunia change from baseline mean: -24.32

	dryness scale used: VAS scale (0-100;LB) dryness baseline mean: 45.92 dryness baseline SD: 17.14 dryness endpoint mean: 16.16 dryness endpoint SD: 13.27 dryness change from baseline mean: -29.76 discomfort scale used: VAS scale (0-100;LB) discomfort baseline mean: 36.68 discomfort baseline SD: 16.23 discomfort endpoint mean: 11.24 discomfort endpoint SD: 10 discomfort change from baseline mean: -25.44

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(Treatments were not blinded to participants or investigators. No information regarding non-adherence provided. Per protocol analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for at least 92% or participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High *(Appropriate measures used however assessors were not blinded to intervention assignment which might have influenced study outcomes.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All outcomes reported and analysed as reported in trial protocol.)*

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	High *(Study had high risk of bias in two domains due to lack of information regarding possible deviations and bias in measurement of outcomes.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Cano, 2012**

Bibliographic Reference Cano, A; Estévez, J; Usandizaga, R; Gallo, J L; Guinot, M; Delgado, J L; Castellanos, E; Moral, E; Nieto, C; del Prado, J M; al., et; The therapeutic effect of a new ultra low concentration estriol gel formulation (0.005% estriol vaginal gel) on symptoms and signs of postmenopausal vaginal atrophy: results from a pivotal phase III study; Menopause (New York, N.Y.); 2012; vol. 19 (no. 10ccgynaecologyandfertility); 1130-1139

3 **Study details**

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Symptoms of vaginal dryness Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRIOL_GEL** Age at study entry, mean (SD) years: 56.5 (5.72) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 9.7 **Arm 2: PLC_TOPICAL**

	Age at study entry, mean (SD) years: 57.2 (6.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 10.2
Intervention(s)/control	**Arm 1: ESTRIOL_GEL** Estriol gel, 50ug **Arm 2: PLC_TOPICAL** Placebo gel Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 167 N completers: 153 Analysis method: ITT ITT imputation method: NR
Outcome data	**Arm 1: ESTRIOL_GEL** N randomised: 114 N completers: 105 discontinuation due to adverse events: 1 discontinuation for any reason: 9 **Arm 2: PLC_TOPICAL** N randomised: 53 N completers: 48 discontinuation due to adverse events: 0 discontinuation for any reason: 5

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on concealment process provided.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded trial with neither participants or personnel aware of intervention assignment.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Nearly all outcome data available (>90%))*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Trial protocol unavailable.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in 2 domains due to insufficient information)*
Overall bias and directness	Overall directness	Directly applicable

2

3 **Chen, 2013**

Bibliographic Reference Chen, Junya; Geng, Li; Song, Xuehong; Li, Hongxia; Giordan, Nicola; Liao, Qinping; Evaluation of the efficacy and safety of hyaluronic acid vaginal gel to ease vaginal dryness: a multicenter, randomized, controlled, open-label, parallel-group, clinical trial; J. Sex. Med.; 2013; vol. 10 (no. 6); 1575-1584

1 **Study details**

Country/ies where study was carried out	China
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Symptoms of vaginal dryness Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: LUBRICANT** Age at study entry, mean (SD) years: 54.05 (4.27) Age at study entry, median (range) years: NR(39.39-65.71) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 4.44 **Arm 2: ESTRIOL_CREAM** Age at study entry, mean (SD) years: 54.41 (4.6) Age at study entry, median (range) years: NR(44.49-67.71) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 5.58
Intervention(s)/control	**Arm 1: LUBRICANT** Hyaluronic acid vaginal gel (Hyalofemme). 0.5g once every 3 days for 30 days **Arm 2: ESTRIOL_CREAM** 0.5g Estriol cream. 0.5g once every 3 days for 30 days Treatment duration (weeks): 4.30 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol
Duration of follow-up	4.3 weeks
Sources of funding	Not reported
Sample size	N randomised: 144 N completers: 133 Analysis method: ITT

	ITT imputation method: LOCF
Outcome data	**Arm 1: LUBRICANT** N randomised: 72 N completers: 67 discontinuation due to adverse events: 1 discontinuation for any reason: 5 dryness scale used: VAS scale (0-10;LB) dryness baseline mean: 5.76 dryness baseline SD: 1.88 dryness endpoint mean: 0.9 dryness endpoint SD: 1.18 dryness change from baseline mean: -4.86 **Arm 2: ESTRIOL_CREAM** N randomised: 72 N completers: 66 discontinuation due to adverse events: 3 discontinuation for any reason: 6 dryness scale used: VAS scale (0-10;LB) dryness baseline mean: 5.26 dryness baseline SD: 1.82 dryness endpoint mean: 0.62 dryness endpoint SD: 1.06 dryness change from baseline mean: -4.64

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation process with no differences at baseline between groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Open label study with no information regarding deviations. Appropriate ITT analysis was used.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for at least 91.7% of participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High *(Open label study with participants aware of their assigned intervention and self-rated assessments were used.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available.)*
Overall bias and directness	Risk of bias judgement	High *(Study rated high risk in one domain due to risk of bias in measurement of outcomes.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Chompootaweep, 1998**

Bibliographic Reference Chompootaweep, S; Nunthapisud, P; Trivijitsilp, P; Sentrakul, P; Dusitsin, N; The use of two estrogen preparations (a combined contraceptive pill versus conjugated estrogen cream) intravaginally to treat urogenital symptoms in postmenopausal Thai women: a comparative study; Clin. Pharmacol. Ther.; 1998; vol. 64 (no. 2); 204-210

3 **Study details**

Country/ies where study was carried out	Thailand
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: urogenital sumptoms (defined as vaginal dryness, burning, itching, dyspareunia, dysuria, etc) Scale used to assess GU symptom severity for trial entry: Self-reported

	Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: LEV_ESTRADIOL_TAB** Age at study entry, mean (SD) years: 54.2 (4.9) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 6 **Arm 2: ESTRADIOL_CREAM** Age at study entry, mean (SD) years: 54.7 (4) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 7
Intervention(s)/control	**Arm 1: LEV_ESTRADIOL_TAB** 250ug levonorgestrel + 30ug ethinyl estradiol tablet - take intravaginally. **Arm 2: ESTRADIOL_CREAM** 0.625mg estradiol cream Treatment duration (weeks): 8 Lubricant/moisturizer permitted: NR
Duration of follow-up	8 weeks
Sources of funding	Industry funded
Sample size	N randomised: 40 N completers: 40 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: LEV_ESTRADIOL_TAB** N randomised: 20 N completers: 20 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: 4-point scale (0-3;LB)

	dyspareunia baseline mean: 2.86 dyspareunia baseline SD: 0.36 dyspareunia endpoint mean: 0 dyspareunia endpoint SD: 0 dyspareunia change from baseline mean: -2.86 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.85 dryness baseline SD: 0.37 dryness endpoint mean: 0 dryness endpoint SD: 0 dryness change from baseline mean: -2.85 **Arm 2: ESTRADIOL_CREAM** N randomised: 20 N completers: 20 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.83 dyspareunia baseline SD: 0.58 dyspareunia endpoint mean: 0 dyspareunia endpoint SD: 0 dyspareunia change from baseline mean: -2.83 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.55 dryness baseline SD: 0.94 dryness endpoint mean: 0 dryness endpoint SD: 0 dryness change from baseline mean: -2.55

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information regarding concealment method provided.)*

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(No information regarding drop out or adherence to intervention. Per protocol analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(No information regarding drop outs provided.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures were used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available.)*
Overall bias and directness	Risk of bias judgement	High *(Study had high risk of bias in two domains due to missing information regarding drop outs.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Constantine, 2017**

Bibliographic Reference Constantine, Ginger D; Bouchard, Celine; Pickar, James H; Archer, David F; Graham, Shelli; Bernick, Brian; Mirkin, Sebastian; Consistency of Effect with a Low-Dose, Estradiol Vaginal Capsule (TX-004HR): Evaluating Improvement in Vaginal Physiology and Moderate-to-Severe Dyspareunia in Subgroups of Postmenopausal Women.; Journal of women's health (2002); 2017; vol. 26 (no. 6); 616-623

1 **Study details**

Country/ies where study was carried out	US/Canada
Inclusion / exclusion criteria	GU symptom inclusion criteria: moderate to severe dyspareunia Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_GELCAP** Age at study entry, mean (SD) years: 58.6 (6.3) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 14.3 **Arm 2: PLC_PESSARY** Age at study entry, mean (SD) years: 59.4 (6) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 13.9
Intervention(s)/control	**Arm 1: ESTRADIOL_GELCAP** f TX-004HR vaginal estradiol (10µg) soft-gel capsules **Arm 2: PLC_PESSARY** Placebo vaginal capsule Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 375 N completers: 351 Analysis method: mITT ITT imputation method: mixed-effects model for repeated measures (no LOCF)

Outcome data	**Arm 1: ESTRADIOL_GELCAP** N randomised: 188 N completers: 174 discontinuation due to adverse events: 3 discontinuation for any reason: 14 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.6 dyspareunia baseline SD: 0.5 dyspareunia endpoint mean: 0.91 dyspareunia endpoint SD: 0.9 dyspareunia change from baseline mean: -1.69 dyspareunia change from baseline SD: 0.89 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: -1.5 dryness baseline SD: 0.5 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: -0.8 discomfort baseline SD: 0.86 **Arm 2: PLC_PESSARY** N randomised: 187 N completers: 177 discontinuation due to adverse events: 3 discontinuation for any reason: 10 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.7 dyspareunia baseline SD: 0.5 dyspareunia endpoint mean: 1.42 dyspareunia endpoint SD: 1.1 dyspareunia change from baseline mean: -1.28 dyspareunia change from baseline SD: 0.89 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: -1 dryness baseline SD: 0.45 discomfort scale used: 4-point scale (0-3;LB)

	discomfort baseline mean: -0.6 discomfort baseline SD: 0.76

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed allocation method with no differences at baseline between groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with appropriate modified ITT analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for 92% of participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used. Unknown if assessors were aware of assigned intervention but unlikely to have influenced outcomes.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data was reported and analysed according to trial protocol.)*
Overall bias and directness	Risk of bias judgement	Low *(Study had low risk of bias in all domains.)*
Overall bias and directness	Overall directness	Directly applicable

Cruz, 2018

Bibliographic Reference	Cruz, Vera L; Steiner, Marcelo L; Pompei, Luciano M; Strufaldi, Rodolfo; Fonseca, Fernando L Afonso; Santiago, Lucila H Simardi; Wajsfeld, Tali; Fernandes, Cesar E; Randomized, double-blind, placebo-controlled clinical trial for evaluating the

efficacy of fractional CO2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women.; Menopause (New York, N.Y.); 2018; vol. 25 (no. 1); 21-28

1 **Study details**

Country/ies where study was carried out	Brazil
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: one moderate symptom of VVA Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: CO2_LASER** Age at study entry, mean (SD) years: 55.9 (5.2) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 8.2 **Arm 2: ESTRIOL_CREAM** Age at study entry, mean (SD) years: 56.9 (6) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 8.7 **Arm 3: CO2_LASER + ESTRIOL_CREAM** Age at study entry, mean (SD) years: 55.7 (4.4) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 8.3
Intervention(s)/control	**Arm 1: CO2_LASER** CO2 vaginal laser (SmartXide2 system, MonaLisa Touch) + placebo vaginal cream Treatment intensity: 2 treatments at weeks 0 and 4 **Arm 2: ESTRIOL_CREAM** sham laser treatment (same intravaginal & vulvar probes but no pulse delivered) + vaginal estriol cream **Arm 3: CO2_LASER + ESTRIOL_CREAM**

	CO2 vaginal laser (SmartXide2 system, MonaLisa Touch) + estriol cream 3x/week for 20 weeks Treatment intensity: 2 treatments at weeks 0 and 4 Treatment duration (weeks): 20 Lubricant/moisturizer permitted: No
Duration of follow-up	20 weeks
Sources of funding	Not Industry funded
Sample size	N randomised: 45 N completers: 42 Analysis method: ITT ITT imputation method: NR
Outcome data	**Arm 1: CO2_LASER** N randomised: 15 N completers: 13 discontinuation due to adverse events: 0 discontinuation for any reason: 2 dyspareunia scale used: VAS scale (0-10;LB) dyspareunia baseline mean: 4.9 dyspareunia baseline SD: 3.7 dyspareunia endpoint mean: 0.7 dyspareunia endpoint SD: 1.5 dyspareunia change from baseline mean: -4.2 dryness scale used: VAS scale (0-10;LB) dryness baseline mean: 8 dryness baseline SD: 2.6 dryness endpoint mean: 1.4 dryness endpoint SD: 2 dryness change from baseline mean: -6.6 discomfort scale used: VAS scale (0-10;LB) discomfort baseline mean: 3.9 discomfort baseline SD: 4.5 discomfort endpoint mean: 0.5 discomfort endpoint SD: 1.5

	discomfort change from baseline mean: -3.4 **Arm 2: ESTRIOL_CREAM** N randomised: 15 N completers: 14 discontinuation due to adverse events: 0 discontinuation for any reason: 1 dyspareunia scale used: VAS scale (0-10;LB) dyspareunia baseline mean: 3.2 dyspareunia baseline SD: 3.4 dyspareunia endpoint mean: 0.2 dyspareunia endpoint SD: 0.6 dyspareunia change from baseline mean: -3 dryness scale used: VAS scale (0-10;LB) dryness baseline mean: 5.6 dryness baseline SD: 2.9 dryness endpoint mean: 0.5 dryness endpoint SD: 1.4 dryness change from baseline mean: -5.1 discomfort scale used: VAS scale (0-10;LB) discomfort baseline mean: 0.9 discomfort baseline SD: 1.6 discomfort endpoint mean: 0.1 discomfort endpoint SD: 0.3 discomfort change from baseline mean: -0.8 **Arm 3: CO2_LASER + ESTRIOL_CREAM** N randomised: 15 N completers: 15 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: VAS scale (0-10;LB) dyspareunia baseline mean: 6.5 dyspareunia baseline SD: 3.9 dyspareunia endpoint mean: 0.9 dyspareunia endpoint SD: 1.8 dyspareunia change from baseline mean: -5.6 dryness scale used: VAS scale (0-10;LB)

	dryness baseline mean: 7.9 dryness baseline SD: 3 dryness endpoint mean: 0.3 dryness endpoint SD: 0.7 dryness change from baseline mean: -7.6 discomfort scale used: VAS scale (0-10;LB) discomfort baseline mean: 4.9 discomfort baseline SD: 3.8 discomfort endpoint mean: 0.4 discomfort endpoint SD: 1.1 discomfort change from baseline mean: -4.5

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Concealed randomisation with differences at baseline between groups found (Burning symptoms significantly lower in estriol only group).)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded trial with ITT analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for at least 86% of participants however ITT analysis was used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Urinary incontinence symptoms were not reported according to trial protocol.)*
Overall bias and directness	Risk of bias judgement	Some concerns

Section	Question	Answer
		(Study had some concerns in two domains due to differences at baseline and not reporting all outcome data according to the trial protocol.)
Overall bias and directness	Overall directness	Directly applicable

1

2 **Dugal, 2000**

Bibliographic Reference Dugal, R; Hesla, K; Sørdal, T; Aase, K H; Lilleeidet, O; Wickstrøm, E; Comparison of usefulness of estradiol vaginal tablets and estriol vagitories for treatment of vaginal atrophy; Acta obstetricia et gynecologica Scandinavica; 2000; vol. 79 (no. 4ccgynaecologyandfertility); 293-297

3 **Study details**

Country/ies where study was carried out	Norway
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: symptoms of vaginal atrophy Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_TAB** Age at study entry, mean (SD) years: 58.2 (4.9) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 49.2 Time since menopause at study entry, mean years: NR **Arm 2: ESTRIOL_PESS_50** Age at study entry, mean (SD) years: 59.3 (5.3) Age at study entry, median (range) years: NR(NR-NR)

	Age at menopause, mean years: 49.9 Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRADIOL_TAB** Estradiol vaginal tablets, 25ug, , daily for 2 weeks then 2 tablets weekly **Arm 2: ESTRIOL_PESS_50** Estriol suppositories, 0.5mg, , daily for 2 weeks then 2 pessaries weekly Treatment duration (weeks): 24 Lubricant/moisturizer permitted: NR
Duration of follow-up	24 weeks
Sources of funding	Not reported
Sample size	N randomised: 96 N completers: 85 Analysis method: ITT ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_TAB** N randomised: 48 N completers: 42 discontinuation due to adverse events: 3 discontinuation for any reason: 6 dryness scale used: VAS scale (0-10;LB) dryness baseline mean: 6.06 dryness baseline SD: 1.7 dryness endpoint mean: -4.36 **Arm 2: ESTRIOL_PESS_50** N randomised: 48 N completers: 43 discontinuation due to adverse events: 0 discontinuation for any reason: 5 dryness scale used: VAS scale (0-10;LB) dryness baseline mean: 5.04 dryness baseline SD: 0.8

	dryness endpoint mean: -4.24

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Lack of information about randomisation process and prior HRT use appeared unbalanced between treatment arms.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Analysis was intent-to-treat. Trial was single-blinded - participants were aware of their treatment and it was self-administered)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(Drop out rate was approximately 10% in both groups. It is unclear how many were included for the dryness outcome at 24 weeks follow-up.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Pathological outcomes were assessed by a cytopathologist who was blinded to the allocation. However symptom severity was self-assessed by the patients.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Mean results only reported for vaginal dryness because there was a significant difference. Irritation, itching, dyspareunia, libido, and dysuria only reported as not significant.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(See above)*
Overall bias and directness	Overall directness	Directly applicable

1 **Eriksen, 1992**

Bibliographic Reference	Eriksen, P S; Rasmussen, H; Low-dose 17 beta-estradiol vaginal tablets in the treatment of atrophic vaginitis: a double-blind placebo controlled study; Eur. J. Obstet. Gynecol. Reprod. Biol.; 1992; vol. 44 (no. 2); 137-144

2 **Study details**

Country/ies where study was carried out	Denmark
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: symptoms of vaginal atrophy Scale used to assess GU symptom severity for trial entry: NR Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_TAB** Age at study entry, mean (SD) years: 58.1 (6) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: PLC_PESSARY** Age at study entry, mean (SD) years: 58.6 (6) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRADIOL_TAB** Estradiol vaginal tablets, 25ug (Vagifem) **Arm 2: PLC_PESSARY** Placebo tablets Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks

Sources of funding	Not reported
Sample size	N randomised: 154 N completers: 144 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_TAB** N randomised: 75 N completers: 69 discontinuation due to adverse events: 5 discontinuation for any reason: 6 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 1.29 dyspareunia baseline SD: 1.11 dyspareunia endpoint mean: 0.35 dyspareunia endpoint SD: 0.73 dyspareunia change from baseline mean: -0.95 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.94 dryness baseline SD: 0.92 dryness endpoint mean: 0.57 dryness endpoint SD: 0.9 dryness change from baseline mean: -1.37 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 1.47 discomfort baseline SD: 1.01 discomfort endpoint mean: 0.47 discomfort endpoint SD: 0.81 discomfort change from baseline mean: -1 **Arm 2: PLC_PESSARY** N randomised: 79 N completers: 75 discontinuation due to adverse events: 3 discontinuation for any reason: 4

	dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 1.34 dyspareunia baseline SD: 1.12 dyspareunia endpoint mean: 0.87 dyspareunia endpoint SD: 1.01 dyspareunia change from baseline mean: -0.48 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.82 dryness baseline SD: 0.98 dryness endpoint mean: 1.05 dryness endpoint SD: 1 dryness change from baseline mean: -0.77 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 1.24 discomfort baseline SD: 1.07 discomfort endpoint mean: 0.82 discomfort endpoint SD: 1.05 discomfort change from baseline mean: -0.42

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation concealment provided.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Participants and people delivering the interventions were unaware of assignment.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Nearly all outcome data available (>92%).)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(No information provided on if assessors were blinded or not however this would have unlikely influence the*

Section	Question	Answer
		outcome of assessment.)
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available, therefore unsure if pre-analysis plan was adhered to.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in 2 domains due to insufficient information.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Fernandes, 2014**

Bibliographic Reference Fernandes, T; Costa-Paiva, L H; Pinto-Neto, A M; Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial; Journal of sexual medicine; 2014; vol. 11 (no. 5ccgynaecologyandfertility); 1262-1270

3 **Study details**

Country/ies where study was carried out	Brazil
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: symptoms of vaginal atrophy Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: MOISTURISER** Age at study entry, mean (SD) years: 57 (5.4) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR

	Time since menopause at study entry, mean years: 8.9 **Arm 2: TESTOSTERONE_CREAM** Age at study entry, mean (SD) years: 56.2 (5.3) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 10.3 **Arm 3: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 56.4 (4.8) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 8.1 **Arm 4: LUBRICANT** Age at study entry, mean (SD) years: 57.7 (4.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 9.3
Intervention(s)/control	**Arm 1: MOISTURISER** polyacrylic acid vaginal cream (Vagidrat) **Arm 2: TESTOSTERONE_CREAM** testosterone vaginal cream, 300ug **Arm 3: CONJ_ESTROGEN_CREAM** conjugated estrogen 0.625mg vaginal cream **Arm 4: LUBRICANT** glycerin gel Treatment duration (weeks): 12 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol
Duration of follow-up	12 weeks
Sources of funding	Not Industry funded
Sample size	N randomised: 80 N completers: 76 Analysis method: ITT

	ITT imputation method: NR
Outcome data	**Arm 1: MOISTURISER** N randomised: 20 N completers: 19 discontinuation due to adverse events: 0 discontinuation for any reason: 1 dyspareunia scale used: tFSFI - transformed FSFI pain domain (0-6;LB) dyspareunia baseline mean: 3.4 dyspareunia baseline SD: 2.1 dyspareunia endpoint mean: 1.7 dyspareunia endpoint SD: 2.6 dyspareunia change from baseline mean: -1.7 dryness scale used: tFSFI - transformed FSFI lubrication domain (0-6;LB) dryness baseline mean: 3.1 dryness baseline SD: 2.2 dryness endpoint mean: 1.6 dryness endpoint SD: 2.4 dryness change from baseline mean: -1.5 **Arm 2: TESTOSTERONE_CREAM** N randomised: 20 N completers: 19 discontinuation due to adverse events: 0 discontinuation for any reason: 1 dyspareunia scale used: tFSFI - transformed FSFI pain domain (0-6;LB) dyspareunia baseline mean: 4.5 dyspareunia baseline SD: 1.6 dyspareunia endpoint mean: 1.7 dyspareunia endpoint SD: 2.6 dyspareunia change from baseline mean: -2.8 dryness scale used: tFSFI - transformed FSFI lubrication domain (0-6;LB) dryness baseline mean: 4.4 dryness baseline SD: 1.6 dryness endpoint mean: 2.1 dryness endpoint SD: 2.7 dryness change from baseline mean: -2.3

	Arm 3: CONJ_ESTROGEN_CREAM N randomised: 20 N completers: 18 discontinuation due to adverse events: 1 discontinuation for any reason: 2 dyspareunia scale used: tFSFI - transformed FSFI pain domain (0-6;LB) dyspareunia baseline mean: 4.7 dyspareunia baseline SD: 2 dyspareunia endpoint mean: 3 dyspareunia endpoint SD: 2.9 dyspareunia change from baseline mean: -1.7 dryness scale used: tFSFI - transformed FSFI lubrication domain (0-6;LB) dryness baseline mean: 4.5 dryness baseline SD: 2 dryness endpoint mean: 3.2 dryness endpoint SD: 2.9 dryness change from baseline mean: -1.3 **Arm 4: LUBRICANT** N randomised: 20 N completers: 20 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: tFSFI - transformed FSFI pain domain (0-6;LB) dyspareunia baseline mean: 3.9 dyspareunia baseline SD: 2.1 dyspareunia endpoint mean: 2.9 dyspareunia endpoint SD: 2.4 dyspareunia change from baseline mean: -1 dryness scale used: tFSFI - transformed FSFI lubrication domain (0-6;LB) dryness baseline mean: 4.1 dryness baseline SD: 1.6 dryness endpoint mean: 3.12 dryness endpoint SD: 2.22 dryness change from baseline mean: -0.98

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(*Participants were randomised using a computerised randomisation method and allocation was concealed. *.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(ITT analysis was used and no deviations from the intended intervention arose.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for nearly all participants (>95%))*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High *(Participants self-rated the assessments and were aware of intervention received.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Unable to obtain trial protocol.)*
Overall bias and directness	Risk of bias judgement	High *(Study had high concerns in risk of bias in outcome measures.)*
Overall bias and directness	Overall directness	Directly applicable

Garcia de Arriba, 2022

Bibliographic Reference Garcia de Arriba, Susana; Gruntkemeier, Lisa; Hauser, Manuel; May, Theodor W; Masur, Clarissa; Stute, Petra; Vaginal hormone-free moisturising cream is not inferior to an estriol cream for treating symptoms of vulvovaginal atrophy: Prospective, randomised study.; PloS one; 2022; vol. 17 (no. 5); e0266633

1 **Study details**

Country/ies where study was carried out	Germany/Switzerland
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Vulvovaginal dryness moderate or severe Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: ESTRIOL_CREAM** Age at study entry, mean (SD) years: 61.7 (6.9) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: MOISTURISER** Age at study entry, mean (SD) years: 59.5 (7.3) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRIOL_CREAM** Ovestin estriol cream 1mg estriol in 1g cream - once daily for first 3 weeks then twice weekly **Arm 2: MOISTURISER** Vagisan moisturizing cream intravaginally once per day, outer genital area several times per day as needed Treatment duration (weeks): 6.14 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol
Duration of follow-up	6.14 weeks
Sources of funding	Industry funded
Sample size	N randomised: 172 N completers: 162 Analysis method: Per protocol (n=151)

	ITT imputation method: NR
Outcome data	**Arm 1: ESTRIOL_CREAM** N randomised: 85 N completers: 78 discontinuation due to adverse events: 4 discontinuation for any reason: 7 dyspareunia scale used: 5-point scale (0-4;LB) dyspareunia baseline mean: 2.68 dyspareunia baseline SD: 1.25 dyspareunia endpoint mean: 0.48 dyspareunia endpoint SD: 0.69 dyspareunia change from baseline mean: -2.2 dyspareunia change from baseline SD: 2.98 dryness scale used: 5-point scale (0-4;LB) dryness baseline mean: 2.3 dryness baseline SD: 0.9 **Arm 2: MOISTURISER** N randomised: 87 N completers: 84 discontinuation due to adverse events: 0 discontinuation for any reason: 3 dyspareunia scale used: 5-point scale (0-4;LB) dyspareunia baseline mean: 2.62 dyspareunia baseline SD: 1.19 dyspareunia endpoint mean: 0.92 dyspareunia endpoint SD: 0.96 dyspareunia change from baseline mean: -1.7 dyspareunia change from baseline SD: 1.43 dryness scale used: 5-point scale (0-4;LB) dryness baseline mean: 2.3 dryness baseline SD: 0.8

1 **Critical appraisal**

Section	Question	Answer

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(Open label trial with drop out rate in estriol cream group higher than in non hormonal cream. Completer analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Dropout rate in estriol only group higher with majority of reasons for drop out being adverse affects to the cream.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High *(Appropriate outcome measures were used however outcome measures were self-rated by participants who were aware of their assigned intervention.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Study reported and analysed all outcomes according to trial protocol.)*
Overall bias and directness	Risk of bias judgement	High *(Study was at high risk of bias in three domains mainly due to larger dropout rates in estriol group and lack of appropriate analysis.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Griesser, 2012**

Bibliographic Reference Griesser, H; Skonietzki, S; Fischer, T; Fielder, K; Suesskind, M; Low dose estriol pessaries for the treatment of vaginal atrophy: a double-blind placebo-controlled trial investigating the efficacy of pessaries containing 0.2 mg and 0.03 mg estriol; Maturitas; 2012; vol. 71 (no. 4ccgynaecologyandfertility); 360-368

1 **Study details**

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: symptoms of vaginal atrophy Scale used to assess GU symptom severity for trial entry: Clinical diagnosis Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRIOL_PESS** Age at study entry, mean (SD) years: 64.9 (8.1) Age at study entry, median (range) years: 65 (44-87) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: ESTRIOL_PESS** Age at study entry, mean (SD) years: 65.4 (7.3) Age at study entry, median (range) years: 66 (49-82) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 3: PLC_PESSARY** Age at study entry, mean (SD) years: 64.8 (7.8) Age at study entry, median (range) years: 65 (47-87) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRIOL_PESS** estriol pessary, 0.2mg, once daily application for 20 days, then 2x/week **Arm 2: ESTRIOL_PESS** estriol pessary, 0.03mg, once daily application for 20 days, then 2x/week **Arm 3: PLC_PESSARY** Placebo pessary, once daily application for 20 days, then 2x/week Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR

Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 436 N completers: 395 Analysis method: ITT ITT imputation method: LOCF
Outcome data	**Arm 1: ESTRIOL_PESS** N randomised: 142 N completers: 128 discontinuation due to adverse events: 9 discontinuation for any reason: 14 dryness scale used: VAS scale (0-100;LB) dryness baseline mean: 69.5 dryness baseline SD: 20.2 **Arm 2: ESTRIOL_PESS** N randomised: 147 N completers: 133 discontinuation due to adverse events: 7 discontinuation for any reason: 14 dryness scale used: VAS scale (0-100;LB) dryness baseline mean: 68.7 dryness baseline SD: 20.2 **Arm 3: PLC_PESSARY** N randomised: 147 N completers: 134 discontinuation due to adverse events: 9 discontinuation for any reason: 13 dryness scale used: VAS scale (0-100;LB) dryness baseline mean: 68.7 dryness baseline SD: 19.6

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information about concealment provided)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Trial was double blinded with appropriate analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for at least 90.5% of randomised participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used with assessors blinded to received intervention.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Registered protocol does not provide information on analysis plan.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study showed some concerns in three domains mainly due to missing information.)*
Overall bias and directness	Overall directness	Directly applicable

Henriksson, 1994

Bibliographic Reference Henriksson, L; Stjernquist, M; Boquist, L; Alander, U; Selinus, I; A comparative multicenter study of the effects of continuous low-dose estradiol released from a new vaginal ring versus estriol vaginal pessaries in postmenopausal women with symptoms and signs of urogenital atrophy; Am. J. Obstet. Gynecol.; 1994; vol. 171 (no. 3); 624-632

1 **Study details**

Country/ies where study was carried out	Sweden/Finland/Denmark
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: symptoms of vaginal atrophy Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_RING** Age at study entry, mean (SD) years: 59.2 (6.5) Age at study entry, median (range) years: NR(45-77) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 9.5 **Arm 2: ESTRIOL_PESS_50** Age at study entry, mean (SD) years: 59.8 (7.2) Age at study entry, median (range) years: NR(46-80) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 10.3
Intervention(s)/control	**Arm 1: ESTRADIOL_RING** estradiol vaginal ring, 2mg **Arm 2: ESTRIOL_PESS_50** estriol pessary, 0.5mg, once daily application for first 3 weeks, then 2x/week Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Not reported
Sample size	N randomised: 165 N completers: 157 Analysis method: ITT

	ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_RING** N randomised: 112 N completers: 106 discontinuation due to adverse events: 4 discontinuation for any reason: 6 **Arm 2: ESTRIOL_PESS_50** N randomised: 53 N completers: 51 discontinuation due to adverse events: 1 discontinuation for any reason: 2

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on concealment provided.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and people delivering the intervention were aware of assignment and deviations are unclear.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(Not all data available (less than 90%) with insufficient information regarding missing outcome data.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns *(No information provided if outcome assessors were aware of intervention received. Unclear if results could have been influenced by this.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available.)*

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	High *(Study had some concerns in all domains due to missing information.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Hirschberg, 2020**

Bibliographic Reference Hirschberg, Angelica Linden; Sanchez-Rovira, Pedro; Presa-Lorite, Jesus; Campos-Delgado, Miriam; Gil-Gil, Miguel; Lidbrink, Elisabet; Suarez-Almarza, Javier; Nieto-Magro, Concepcion; Efficacy and safety of ultra-low dose 0.005% estriol vaginal gel for the treatment of vulvovaginal atrophy in postmenopausal women with early breast cancer treated with nonsteroidal aromatase inhibitors: a phase II, randomized, double-blind, placebo-controlled trial.; Menopause (New York, N.Y.); 2020; vol. 27 (no. 5); 526-534

3 **Study details**

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vaginal dryness Scale used to assess GU symptom severity for trial entry: FDA guidelines for drug development (2003) Uterus or not: Both uterus & no uterus Breast or gynae cancer history: Breast cancer
Patient characteristics	**Arm 1: ESTRIOL_GEL** Age at study entry, mean (SD) years: 58.9 (7.6) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: MOISTURISER**

	Age at study entry, mean (SD) years: 61.4 (4.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRIOL_GEL** 0.005% estriol vaginal gel **Arm 2: MOISTURISER** moisturizing gel. 1 g of gel per application for 12 weeks: once daily during the first three weeks, and then twice weekly Treatment duration (weeks): 12 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 61 N completers: 52 Analysis method: ITT ITT imputation method: LOCF
Outcome data	**Arm 1: ESTRIOL_GEL** N randomised: 50 N completers: 43 discontinuation due to adverse events: 1 discontinuation for any reason: 7 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: -1.6 dyspareunia baseline SD: 1 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: -1.8 dryness baseline SD: 0.9 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: -0.7 discomfort baseline SD: 1.3 **Arm 2: MOISTURISER**

	N randomised: 11 N completers: 9 discontinuation due to adverse events: 0 discontinuation for any reason: 2 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: -1.1 dyspareunia baseline SD: 1.1 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: -0.9 dryness baseline SD: 1 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: -0.3 discomfort baseline SD: 1.2

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded trial with appropriate ITT analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures were used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Trial protocol not available.)*

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain due to missing trial protocol information.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Labrie, 2009**

Bibliographic Reference Labrie, Fernand; Archer, David; Bouchard, Céline; Fortier, Michel; Cusan, Leonello; Gomez, José-Luis; Girard, Ginette; Baron, Mira; Ayotte, Normand; Moreau, Michèle; Dubé, Robert; Côté, Isabelle; Labrie, Claude; Lavoie, Lyne; Berger, Louise; Gilbert, Lucy; Martel, Céline; Balser, John; Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy; Menopause; 2009; vol. 16 (no. 5); 907-922

3 **Study details**

Country/ies where study was carried out	Canada
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate or severe vaginal dryness/irritation/dyspareunia Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: PRASTERONE_LOW_DOSE** Age at study entry, mean (SD) years: NR(NR) Age at study entry, median (range) years: 57 (42-72) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: PRASTERONE** Age at study entry, mean (SD) years: NR(NR)

	Age at study entry, median (range) years: 58 (50-74) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 3: PRASTERONE_HIGH_DOSE** Age at study entry, mean (SD) years: NR(NR) Age at study entry, median (range) years: 59 (46-69) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 4: PLC_PESSARY** Age at study entry, mean (SD) years: NR(NR) Age at study entry, median (range) years: 58 (49-70) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: PRASTERONE_LOW_DOSE** Prasterone ovule, 3.25mg **Arm 2: PRASTERONE** Prasterone ovule, 6.5mg **Arm 3: PRASTERONE_HIGH_DOSE** Prasterone ovule, 13mg **Arm 4: PLC_PESSARY** Placebo Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 216 N completers: NR Analysis method: ITT ITT imputation method: LOCF
Outcome data	**Arm 1: PRASTERONE_LOW_DOSE** N randomised: 53

	N completers: NR discontinuation due to adverse events: NR discontinuation for any reason: NR dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.4 dyspareunia baseline SD: 0.87 dyspareunia endpoint mean: 1.2 dyspareunia endpoint SD: 1.09 dyspareunia change from baseline mean: -1.2 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.9 dryness baseline SD: 0.66 dryness endpoint mean: 0.8 dryness endpoint SD: 0.95 dryness change from baseline mean: -1.1 **Arm 2: PRASTERONE** N randomised: 56 N completers: NR discontinuation due to adverse events: NR discontinuation for any reason: NR dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.5 dyspareunia baseline SD: 0.75 dyspareunia endpoint mean: 0.99 dyspareunia endpoint SD: 1.27 dyspareunia change from baseline mean: -1.51 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2 dryness baseline SD: 0.82 dryness endpoint mean: 0.6 dryness endpoint SD: 0.82 dryness change from baseline mean: -1.4 **Arm 3: PRASTERONE_HIGH_DOSE** N randomised: 54 N completers: NR discontinuation due to adverse events: NR

	discontinuation for any reason: NR dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.41 dyspareunia baseline SD: 0.81 dyspareunia endpoint mean: 1 dyspareunia endpoint SD: 1.1 dyspareunia change from baseline mean: -1.41 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.91 dryness baseline SD: 0.81 dryness endpoint mean: 0.6 dryness endpoint SD: 0.66 dryness change from baseline mean: -1.31 **Arm 4: PLC_PESSARY** N randomised: 53 N completers: NR discontinuation due to adverse events: NR discontinuation for any reason: NR dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.39 dyspareunia baseline SD: 0.8 dyspareunia endpoint mean: 1.9 dyspareunia endpoint SD: 1.02 dyspareunia change from baseline mean: -0.49 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.8 dryness baseline SD: 0.95 dryness endpoint mean: 1 dryness endpoint SD: 0.87 dryness change from baseline mean: -0.8

1 **Critical appraisal**

Section	Question	Answer

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on concealment method provided.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with appropriate analysis used)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for nearly all participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data reported and analysed as reported in trial protocol.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain due to insufficient information regarding concealment method.)*
Overall bias and directness	Overall directness	Directly applicable

1 **Labrie, 2016**

Bibliographic Reference Labrie, Fernand; Archer, David F; Koltun, William; Vachon, Andrée; Young, Douglas; Frenette, Louise; Portman, David; Montesino, Marlene; Côté, Isabelle; Parent, Julie; Lavoie, Lyne; Beauregard, Adam; Martel, Céline; Vaillancourt, Mario; Balser, John; Moyneur, Érick; Group, V V A Prasterone Research; Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause; Menopause; 2016; vol. 23 (no. 3); 243-256

1 **Study details**

Country/ies where study was carried out	Canada
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: moderate to severe pain with sex Scale used to assess GU symptom severity for trial entry: Self-reported Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: PRASTERONE** Age at study entry, mean (SD) years: 59.5 (NR) Age at study entry, median (range) years: 59 (40-80) Age at menopause, mean years: 45.4 Time since menopause at study entry, mean years: 14.1 **Arm 2: PLC_PESSARY** Age at study entry, mean (SD) years: 59.6 (NR) Age at study entry, median (range) years: 59 (47-75) Age at menopause, mean years: 46.2 Time since menopause at study entry, mean years: 13.4
Intervention(s)/control	**Arm 1: PRASTERONE** Prasterone ovule, 6.5mg **Arm 2: PLC_PESSARY** Placebo Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 482 N completers: 463 Analysis method: ITT

	ITT imputation method: LOCF
Outcome data	**Arm 1: PRASTERONE** N randomised: 325 N completers: 311 discontinuation due to adverse events: 5 discontinuation for any reason: 14 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.54 dyspareunia baseline SD: 0.54 dyspareunia endpoint mean: 1.13 dyspareunia endpoint SD: 0.9 dyspareunia change from baseline mean: -1.41 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.3 dryness baseline SD: 0.54 dryness endpoint mean: 0.86 dryness endpoint SD: 0.9 dryness change from baseline mean: -1.44 **Arm 2: PLC_PESSARY** N randomised: 157 N completers: 152 discontinuation due to adverse events: 3 discontinuation for any reason: 5 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.56 dyspareunia baseline SD: 0.5 dyspareunia endpoint mean: 1.5 dyspareunia endpoint SD: 1 dyspareunia change from baseline mean: -1.06 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.3 dryness baseline SD: 0.5 dryness endpoint mean: 1.13 dryness endpoint SD: 1 dryness change from baseline mean: -1.17

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded trial with appropriate analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for nearly all participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data was collected and analysed as reported in trial protocol.)*
Overall bias and directness	Risk of bias judgement	Low *(Study had low risk of bias in all domains.)*
Overall bias and directness	Overall directness	Directly applicable

2

3 **Li, 2021**

Bibliographic Reference Li, Fiona G; Maheux-Lacroix, Sarah; Deans, Rebecca; Nesbitt-Hawes, Erin; Budden, Aaron; Nguyen, Kimberly; Lim, Claire Y; Song, Sophia; McCormack, Lalla; Lyons, Stephen D; Segelov, Eva; Abbott, Jason A; Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women With Postmenopausal Vaginal Symptoms: A Randomized Clinical Trial.; JAMA; 2021; vol. 326 (no. 14); 1381-1389

1 **Study details**

Country/ies where study was carried out	Australia
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: dyspareunia, burning, itching, or dryness severe enough to need treatment Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Both uterus & no uterus Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: CO2_LASER** Age at study entry, mean (SD) years: 55 (7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 48 Time since menopause at study entry, mean years: 8 **Arm 2: PLC_PHYSICAL** Age at study entry, mean (SD) years: 58 (8) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 49 Time since menopause at study entry, mean years: 6
Intervention(s)/control	**Arm 1: CO2_LASER** fractional microablative co2 laser (SmartXide2V2LR, MonaLisa Touch, DEKA Laser) Treatment intensity: 3 treatments 1 month apart **Arm 2: PLC_PHYSICAL** Sham laser treatment done at minimal energy settings - with no tissue effects. Treatment intensity: 3 treatments 1 month apart Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms
Duration of follow-up	12 weeks
Sources of funding	Not Industry funded

Sample size	N randomised: 85 N completers: 85 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: CO2_LASER** N randomised: 43 N completers: 43 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: VAS scale (0-100;LB) dyspareunia baseline mean: 69 dyspareunia baseline SD: 29.76 dyspareunia endpoint mean: 54 dyspareunia endpoint SD: 34.6 dyspareunia change from baseline mean: -28.8 dyspareunia change from baseline SD: 122.19 dryness scale used: VAS scale (0-100;LB) dryness baseline mean: 68 dryness baseline SD: 29.76 dryness endpoint mean: 49 dryness endpoint SD: 29.88 dryness change from baseline mean: -18 dryness change from baseline SD: 64.63 discomfort scale used: VAS scale (0-100;LB) discomfort baseline mean: 21 discomfort baseline SD: 26.45 discomfort endpoint mean: 6 discomfort endpoint SD: 12.58 discomfort change from baseline mean: -15.4 discomfort change from baseline SD: 60.228840896355059 dysuria scale used: VAS scale (0-100;LB) dysuria baseline mean: 15 dysuria baseline SD: 26.45 dysuria endpoint mean: 4 dysuria endpoint SD: 11.01

	dysuria change from baseline mean: -11.4 dysuria change from baseline SD: 47.81 **Arm 2: PLC_PHYSICAL** N randomised: 42 N completers: 42 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: VAS scale (0-100;LB) dyspareunia baseline mean: 70 dyspareunia baseline SD: 32.67 dyspareunia endpoint mean: 67 dyspareunia endpoint SD: 32.67 dyspareunia change from baseline mean: -4 dyspareunia change from baseline SD: 101.16 dryness scale used: VAS scale (0-100;LB) dryness baseline mean: 71 dryness baseline SD: 27.77 dryness endpoint mean: 59 dryness endpoint SD: 32.67 dryness change from baseline mean: -12 dryness change from baseline SD: 85.03 discomfort scale used: VAS scale (0-100;LB) discomfort baseline mean: 25 discomfort baseline SD: 24.5 discomfort endpoint mean: 14 discomfort endpoint SD: 17.97 discomfort change from baseline mean: -8.3 discomfort change from baseline SD: 53.403770689578252 dysuria scale used: VAS scale (0-100;LB) dysuria baseline mean: 8 dysuria baseline SD: 16.33 dysuria endpoint mean: 8 dysuria endpoint SD: 14.7 dysuria change from baseline mean: 2.2 dysuria change from baseline SD: 37.11

Other	For outcome ‘dyspareunia baseline, endpoint, and change scores’, the technical team noticed errors in the reported values. The values reported here used reported baseline and final scores to calculate change from baseline. (Authors sent updated results, which are similar to calculated value).

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Appropriate measures and analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for 91% of participants)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Some data (treatment discomfort, acceptability, and satisfaction, as well as vaginal lubricant use) reported in the trial protocol was not reported in this article.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain due bias in selection of the reported results.)*
Overall bias and directness	Overall directness	Directly applicable

2

1 **Lima, 2013**

Bibliographic Reference	Lima, S M; Yamada, S S; Reis, B F; Postigo, S; Galvão da Silva, M A; Aoki, T; Effective treatment of vaginal atrophy with isoflavone vaginal gel; Maturitas; 2013; vol. 74 (no. 3cccomplementarymedicine); 252-258

2 **Study details**

Country/ies where study was carried out	Brazil
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Any vulvovaginal symptoms Scale used to assess GU symptom severity for trial entry: Self reported (4-point scale) Uterus or not: Uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: PHYTO_CREAM** Age at study entry, mean (SD) years: 57 (NR) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 49 Time since menopause at study entry, mean years: 9 **Arm 2: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 56 (NR) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 48.5 Time since menopause at study entry, mean years: 6 **Arm 3: PLC_TOPICAL** Age at study entry, mean (SD) years: 57 (NR) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 48 Time since menopause at study entry, mean years: 9
Intervention(s)/control	**Arm 1: PHYTO_CREAM** Isoflavone vaginal gel 4%, 1g, once daily. **Arm 2: CONJ_ESTROGEN_CREAM** CEE vaginal cream, 0.5g, once daily.

	Arm 3: PLC_TOPICAL Placebo cream, 1g, , once daily. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Not Industry funded
Sample size	N randomised: 90 N completers: 75 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: PHYTO_CREAM** N randomised: 30 N completers: 30 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.6 dyspareunia baseline SD: 0.5 dyspareunia endpoint mean: 0.63 dyspareunia endpoint SD: 0.56 dyspareunia change from baseline mean: -1.97 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.7 dryness baseline SD: 0.47 dryness endpoint mean: 0.63 dryness endpoint SD: 0.5 dryness change from baseline mean: -2.07 **Arm 2: CONJ_ESTROGEN_CREAM** N randomised: 30 N completers: 20 discontinuation due to adverse events: 7 discontinuation for any reason: 10

	dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.57 dyspareunia baseline SD: 0.5 dyspareunia endpoint mean: 0.65 dyspareunia endpoint SD: 0.59 dyspareunia change from baseline mean: -1.92 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.6 dryness baseline SD: 0.5 dryness endpoint mean: 0.35 dryness endpoint SD: 0.49 dryness change from baseline mean: -2.25 **Arm 3: PLC_TOPICAL** N randomised: 30 N completers: 25 discontinuation due to adverse events: 0 discontinuation for any reason: 5 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.73 dyspareunia baseline SD: 0.45 dyspareunia endpoint mean: 1.36 dyspareunia endpoint SD: 0.57 dyspareunia change from baseline mean: -1.37 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.73 dryness baseline SD: 0.45 dryness endpoint mean: 1.26 dryness endpoint SD: 0.73 dryness change from baseline mean: -1.4

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation	Risk of bias judgement for the	Some concerns *(No information on concealment process provided.)*

Section	Question	Answer
process	randomisation process	
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Study was double blinded with appropriate analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Large differences in drop-out rates between groups however intent to treat analysis used based on last observation carried forward.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns *(Unclear if assessor were blinded to intervention and how this could have influenced assessments.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in 3 domains mainly due to missing information)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Manonai, 2001**

Bibliographic Reference Manonai, J; Theppisai, U; Suthutvoravut, S; Udomsubpayakul, U; Chittacharoen, A; The effect of estradiol vaginal tablet and conjugated estrogen cream on urogenital symptoms in postmenopausal women: a comparative study; Journal of obstetrics and gynaecology research; 2001; vol. 27 (no. 5ccgynaecologyandfertility); 255-260

3 **Study details**

Country/ies where	Thailand

study was carried out	
Inclusion / exclusion criteria	GU symptom inclusion criteria: Any urogenital symptoms Scale used to assess GU symptom severity for trial entry: NR Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_TAB** Age at study entry, mean (SD) years: 55.1 (4.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 48.9 Time since menopause at study entry, mean years: 6.2 **Arm 2: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 55.8 (4.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 49.3 Time since menopause at study entry, mean years: 6.3
Intervention(s)/control	**Arm 1: ESTRADIOL_TAB** Vaginal estradiol tablet (25Âµg estradiol), daily for 2 weeks then twice weekly for 10 weeks. **Arm 2: CONJ_ESTROGEN_CREAM** CEE vaginal cream. 1g (0.625 mg CEE) daily for 2 weeks then twice weekly for 10 weeks. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Not reported
Sample size	N randomised: 53 N completers: 48 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_TAB** N randomised: 27

	N completers: 24 discontinuation due to adverse events: 1 discontinuation for any reason: 3 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 1.88 dyspareunia baseline SD: 0.9 dyspareunia endpoint mean: 0.45 dyspareunia endpoint SD: 0.72 dyspareunia change from baseline mean: -1.43 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.13 dryness baseline SD: 0.45 dryness endpoint mean: 0.5 dryness endpoint SD: 0.51 dryness change from baseline mean: -1.63 **Arm 2: CONJ_ESTROGEN_CREAM** N randomised: 26 N completers: 24 discontinuation due to adverse events: 2 discontinuation for any reason: 2 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 1.79 dyspareunia baseline SD: 1.06 dyspareunia endpoint mean: 0.12 dyspareunia endpoint SD: 0.33 dyspareunia change from baseline mean: -1.67 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 1.92 dryness baseline SD: 0.58 dryness endpoint mean: 0.17 dryness endpoint SD: 0.38 dryness change from baseline mean: -1.75

1

Critical appraisal

Section	Question		Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process		Some concerns (No information on concealment process.)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)		Low (Study was open label but no deviations arose.)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data		Some concerns (Data available for 90.5% of participants.)
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome		Some concerns (Assessors were aware of intervention assignment.)
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result		Some concerns (No trial protocol available)
Overall bias and directness	Risk of bias judgement		Some concerns (Study had some concerns in three domains mainly due to insufficient information and missing outcome data.)
Overall bias and directness	Overall directness	Directly applicable	

Mitchell, 2018

Bibliographic Reference Mitchell, Caroline M; Reed, Susan D; Diem, Susan; Larson, Joseph C; Newton, Katherine M; Ensrud, Kristine E; LaCroix, Andrea Z; Caan, Bette; Guthrie, Katherine A; Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms: A randomized clinical trial; JAMA Intern. Med.; 2018; vol. 178 (no. 5); 681-690

Study details

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)

Inclusion / exclusion criteria	GU symptom inclusion criteria: moderate to severe vulvovaginal itching, pain, irritation, or dryness Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_TAB** Age at study entry, mean (SD) years: 61 (4) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: MOISTURISER** Age at study entry, mean (SD) years: 61 (4) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 3: PLC_PESSARY** Age at study entry, mean (SD) years: 61 (4) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRADIOL_TAB** Vagifem 10-µg estradiol tablet + placebo vaginal gel. Vaginal tablet daily for 2 weeks, then twice weekly for the remaining 10 weeks, and the vaginal moisturizer every 3 days. **Arm 2: MOISTURISER** Placebo vaginal tablet + Replens vaginal moisturizer. Vaginal tablet daily for 2 weeks, then twice weekly for the remaining 10 weeks, and the vaginal moisturizer every 3 days. **Arm 3: PLC_PESSARY** Placebo tablet + placebo gel Treatment duration (weeks): 12 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol
Duration of follow-up	12 weeks
Sources of funding	Not Industry funded

Sample size	N randomised: 302 N completers: 294 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_TAB** N randomised: 102 N completers: 97 discontinuation due to adverse events: NR discontinuation for any reason: 5 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.5 dyspareunia baseline SD: 0.66 dyspareunia endpoint mean: 1 dyspareunia endpoint SD: -1.5 dyspareunia change from baseline mean: 1.09 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.3 dryness baseline SD: 0.48 dryness endpoint mean: 0.9 dryness endpoint SD: -1.4 dryness change from baseline mean: 0.95 **Arm 2: MOISTURISER** N randomised: 100 N completers: 99 discontinuation due to adverse events: NR discontinuation for any reason: 1 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.5 dyspareunia baseline SD: 0.47 dyspareunia endpoint mean: 1.4 dyspareunia endpoint SD: -1.1 dyspareunia change from baseline mean: 1.39 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.4 dryness baseline SD: 0.46

	dryness endpoint mean: 1.1 dryness endpoint SD: -1.3 dryness change from baseline mean: 0.91 **Arm 3: PLC_PESSARY** N randomised: 100 N completers: 98 discontinuation due to adverse events: NR discontinuation for any reason: 2 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.5 dyspareunia baseline SD: 0.48 dyspareunia endpoint mean: 1 dyspareunia endpoint SD: -1.5 dyspareunia change from baseline mean: 1.16 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.4 dryness baseline SD: 0.68 dryness endpoint mean: 1 dryness endpoint SD: -1.4 dryness change from baseline mean: 0.88

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Double blinded study with no failures in implementing the interventions evident.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for at least 97% of participants.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All data collected, reported and analysed as reported in trial protocol.)*
Overall bias and directness	Risk of bias judgement	Low *(Study rated with low risk of bias in all domains.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Pickar, 2016**

Bibliographic Reference Pickar, James H; Amadio, Julia M; Hill, John M; Bernick, Brian A; Mirkin, Sebastian; A randomized, double-blind, placebo-controlled phase 2 pilot trial evaluating a novel, vaginal softgel capsule containing solubilized estradiol.; Menopause (New York, N.Y.); 2016; vol. 23 (no. 5); 506-10

3 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: moderate-to-severe vaginal dryness, vaginal pain associated with sexual activity, vaginal and/or vulvar irritation/itching, dysuria, or vaginal bleeding associated with sexual activity Scale used to assess GU symptom severity for trial entry: NR Uterus or not: NR Breast or gynae cancer history: NR

Patient characteristics	**Arm 1: ESTRADIOL_GELCAP** Age at study entry, mean (SD) years: 62.4 (5.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: PLC_PESSARY** Age at study entry, mean (SD) years: 62.6 (7.3) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRADIOL_GELCAP** 10mg TX-004HR vaginal E2 softgel vaginal capsules (TherapeuticsMD) intravaginally once-daily for 14 days **Arm 2: PLC_PESSARY** placebo softgel vaginal capsules intravaginally once-daily for 14 days Treatment duration (weeks): 2 Lubricant/moisturizer permitted: NR
Duration of follow-up	2 weeks
Sources of funding	Industry funded
Sample size	N randomised: 50 N completers: 48 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_GELCAP** N randomised: 24 N completers: 24 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.08 dyspareunia baseline SD: 1.28

	dyspareunia endpoint mean: -0.8 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.29 dryness baseline SD: 1.29 dryness endpoint mean: -1 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 0.88 dysuria scale used: 4-point scale (0-3;LB) dysuria baseline mean: 0.58 **Arm 2: PLC_PESSARY** N randomised: 26 N completers: 24 discontinuation due to adverse events: 1 discontinuation for any reason: 2 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: 2.33 dyspareunia baseline SD: 1.83 dyspareunia endpoint mean: -0.5 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: 2.38 dryness baseline SD: 1.68 dryness endpoint mean: -0.7 discomfort scale used: 4-point scale (0-3;LB) discomfort baseline mean: 1.33 dysuria scale used: 4-point scale (0-3;LB) dysuria baseline mean: 0.62

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2b: Risk of bias due to deviations from the	Risk of bias judgement for deviations from the	Low *(Double blinded study with no failures of*

Section	Question	Answer
intended interventions (effect of adhering to intervention)	intended interventions (effect of adhering to intervention)	*implementing interventions apparent.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for at least 92% of participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures used with assessors blinded to intervention assignment,)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study has some concerns in one domain due to lack of information regarding trial protocol.)*
Overall bias and directness	Overall directness	Directly applicable

Poordast, 2021

Bibliographic Reference	Poordast, Tahereh; Ghaedian, Lida; Ghaedian, Leila; Najib, Fatemeh Sadat; Alipour, Shohreh; Hosseinzadeh, Massood; Vardanjani, Hossein Molavi; Salehi, Alireza; Hosseinimehr, Seyed Jalal; Aloe Vera; A new treatment for atrophic vaginitis, A randomized double-blinded controlled trial.; Journal of ethnopharmacology; 2021; vol. 270; 113760

Study details

Country/ies where study was carried out	Iran, Islamic Republic of
Study type	Randomised controlled trial (RCT)

Inclusion / exclusion criteria	GU symptom inclusion criteria: Urogenital symptoms Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: CONJ_ESTROGEN_CREAM** Age at study entry, mean (SD) years: 61.2 (10.28) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 12.73 **Arm 2: LUBRICANT** Age at study entry, mean (SD) years: 59.6 (8.29) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 11.13
Intervention(s)/control	**Arm 1: CONJ_ESTROGEN_CREAM** CEE vaginal cream. 5mg daily (0.62mg CEE per 1g cream) for 2 weeks then 3 times per week for 4 weeks. **Arm 2: LUBRICANT** Aloe vera vaginal gel (2% Aloe vera powder). 5mg daily for 2 weeks then 3 times per week for 4 weeks. Treatment duration (weeks): 6 Lubricant/moisturizer permitted: In specific treatment arms only as part of protocol
Duration of follow-up	6 weeks
Sources of funding	Not Industry funded
Sample size	N randomised: 66 N completers: 60 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: CONJ_ESTROGEN_CREAM** N randomised: 33 N completers: 30 discontinuation due to adverse events: 3

	discontinuation for any reason: 3 dyspareunia scale used: 5-point scale (0-4;LB) dyspareunia baseline mean: 0.93 dyspareunia baseline SD: 0.91 dyspareunia endpoint mean: 0.13 dyspareunia endpoint SD: 0.35 dyspareunia change from baseline mean: -0.8 dryness scale used: 5-point scale (0-4;LB) dryness baseline mean: 1.37 dryness baseline SD: 0.61 dryness endpoint mean: 0.13 dryness endpoint SD: 0.35 dryness change from baseline mean: -1.24 discomfort scale used: 0.53 discomfort baseline mean: 0.63 discomfort baseline SD: 0.07 discomfort endpoint mean: 0.25 discomfort endpoint SD: -0.46 discomfort change from baseline mean: 5-point scale (0-4;LB) dysuria scale used: 5-point scale (0-4;LB) dysuria baseline mean: 0.37 dysuria baseline SD: 0.67 dysuria endpoint mean: 0.23 dysuria endpoint SD: 0.57 dysuria change from baseline mean: -0.14 **Arm 2: LUBRICANT** N randomised: 33 N completers: 30 discontinuation due to adverse events: 0 discontinuation for any reason: 3 dyspareunia scale used: 5-point scale (0-4;LB) dyspareunia baseline mean: 0.97 dyspareunia baseline SD: 1.13 dyspareunia endpoint mean: 0.23 dyspareunia endpoint SD: 0.43 dyspareunia change from baseline mean: -0.74

	dryness scale used: 5-point scale (0-4;LB) dryness baseline mean: 1.07 dryness baseline SD: 0.58 dryness endpoint mean: 0.27 dryness endpoint SD: 0.45 dryness change from baseline mean: -0.8 discomfort scale used: 0.53 discomfort baseline mean: 0.57 discomfort baseline SD: 0.13 discomfort endpoint mean: 0.35 discomfort endpoint SD: -0.4 discomfort change from baseline mean: 5-point scale (0-4;LB) dysuria scale used: 5-point scale (0-4;LB) dysuria baseline mean: 0.53 dysuria baseline SD: 0.9 dysuria endpoint mean: 0.4 dysuria endpoint SD: 0.67 dysuria change from baseline mean: -0.13

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with only difference at baseline between groups being economic status (higher in aloe vera group))*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Double blinded study with no failures of implementation of interventions apparent.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for at least 92% of participants.)*
Domain 4. Bias in measurement of the	Risk of bias judgement for measurement of	Low

Section	Question	Answer
outcome	the outcome	*(Appropriate measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Unable to obtain trial protocol.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain due to unavailable trial protocol)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Portman, 2013**

Bibliographic Reference Portman, David J; Bachmann, Gloria A; Simon, James A; Group, Ospemifene Study; Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy; Menopause; 2013; vol. 20 (no. 6); 623-630

3 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: moderate-to-severe dyspareunia as MBS Scale used to assess GU symptom severity for trial entry: Self reported (4-point scale) Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: OSPEMIFENE** Age at study entry, mean (SD) years: 58 (6.4) Age at study entry, median (range) years: NR(NR-NR)

	Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: PLC-ORAL** Age at study entry, mean (SD) years: 58.1 (6) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: OSPEMIFENE** ospemifene 60 mg oral tablet once daily **Arm 2: PLC-ORAL** placebo oral tablet once daily Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 605 N completers: 544 Analysis method: ITT ITT imputation method: LOCF
Outcome data	**Arm 1: OSPEMIFENE** N randomised: 303 N completers: 278 discontinuation due to adverse events: 14 discontinuation for any reason: 25 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: -1.5 dyspareunia baseline SD: 1.1 **Arm 2: PLC-ORAL** N randomised: 302 N completers: 266 discontinuation due to adverse events: 9

	discontinuation for any reason: 36 dyspareunia scale used: 4-point scale (0-3;LB) dyspareunia baseline mean: -1.2 dyspareunia baseline SD: 1.1

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information regarding concealment process.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with appropriate analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data of 88.1% of participants available however ITT analysis was used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data reported and analysed as reported in trial protocol.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain due to lack of information regarding concealment during randomisation.)*
Overall bias and directness	Overall directness	Directly applicable

1 **Portman, 2014**

Bibliographic Reference Portman, D; Palacios, S; Nappi, R E; Mueck, A O; Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomised, placebo-controlled, phase III trial; Maturitas; 2014; vol. 78 (no. 2); 91-98

2 **Study details**

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: moderate-to-severe vaginal dryness as MBS Scale used to assess GU symptom severity for trial entry: Self reported (4-point scale) Uterus or not: NR Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: OSPEMIFENE** Age at study entry, mean (SD) years: 59.9 (6.7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: PLC_ORAL** Age at study entry, mean (SD) years: 59.3 (7) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: OSPEMIFENE** ospemifene 60 mg oral tablet once daily **Arm 2: PLC_ORAL** placebo oral tablet once daily Treatment duration (weeks): 12 Lubricant/moisturizer permitted: Yes in all treatment arms

Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 314 N completers: 275 Analysis method: ITT ITT imputation method: LOCF
Outcome data	**Arm 1: OSPEMIFENE** N randomised: 160 N completers: 138 discontinuation due to adverse events: 11 discontinuation for any reason: 22 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: -1.3 dryness baseline SD: 1.08 **Arm 2: PLC_ORAL** N randomised: 154 N completers: 137 discontinuation due to adverse events: 5 discontinuation for any reason: 17 dryness scale used: 4-point scale (0-3;LB) dryness baseline mean: -1.1 dryness baseline SD: 1.02

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information regarding concealment process.)*
Domain 2a: Risk of bias due to deviations from	Risk of bias for deviations from the	Low *(Double blinded study with appropriate analysis*

Section	Question	Answer
the intended interventions (effect of assignment to intervention)	intended interventions (effect of assignment to intervention)	*used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data of 88.1% of participants available however ITT analysis was used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data reported and analysed as reported in trial protocol.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain due to insufficient information regarding concealment during randomisation.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Ruanphoo, 2020**

Bibliographic Reference Ruanphoo, Purim; Bunyavejchevin, Suvit; Treatment for vaginal atrophy using microablative fractional CO2 laser: a randomized double-blinded sham-controlled trial.; Menopause (New York, N.Y.); 2020; vol. 27 (no. 8); 858-863

3 **Study details**

Country/ies where study was carried out	Thailand
Inclusion / exclusion criteria	GU symptom inclusion criteria: Moderate to severe vaginal atrophy symptoms Scale used to assess GU symptom severity for trial entry: NR

	Uterus or not: NR Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: CO2_LASER** Age at study entry, mean (SD) years: 61.73 (8.01) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 48.95 **Arm 2: PLC_PHYSICAL** Age at study entry, mean (SD) years: 59.84 (7.49) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 49.47
Intervention(s)/control	**Arm 1: CO2_LASER** Fractional microablative CO2 laser (MonaLisa Touch â„¢, DEKA) treatment Treatment intensity: 3 treatments 1 month apart **Arm 2: PLC_PHYSICAL** Sham laser treatment (same intravaginal & vulvar probes but no pulse delivered) Treatment intensity: 3 treatments 1 month apart Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No
Duration of follow-up	12 weeks
Sources of funding	Not Industry funded
Sample size	N randomised: 88 N completers: 79 Analysis method: ITT ITT imputation method: multiple imputation
Outcome data	**Arm 1: CO2_LASER** N randomised: 44 N completers: 41 discontinuation due to adverse events: 1

	discontinuation for any reason: 3 **Arm 2: PLC_PHYSICAL** N randomised: 44 N completers: 38 discontinuation due to adverse events: 0 discontinuation for any reason: 6

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with appropriate analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Only 86% of data available for control group however appropriate ITT analysis used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used with assessors blinded to intervention assignment)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Unable to obtain trial protocol.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain mainly due in unavailable trial protocol.)*

Section	Question	Answer
Overall bias and directness	Overall directness	Directly applicable

1

2 **Salvatore, 2021**

Bibliographic Reference Salvatore, S; Pitsouni, E; Grigoriadis, T; Zacharakis, D; Pantaleo, G; Candiani, M; Athanasiou, S; CO2 laser and the genitourinary syndrome of menopause: a randomized sham-controlled trial.; Climacteric : the journal of the International Menopause Society; 2021; vol. 24 (no. 2); 187-193

3 **Study details**

Country/ies where study was carried out	Italy/Greece
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Genitourinal syndrome of menopause with vaginal dryness or dyspareunia as MBS Scale used to assess GU symptom severity for trial entry: International Society for the Study of Women's Sexual Health and The North American Menopause Society Uterus or not: NR Breast or gynae cancer history: None
Patient characteristics	**Arm 1: CO2_LASER** Age at study entry, mean (SD) years: 57 (6.9) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 48.7 Time since menopause at study entry, mean years: 8.2 **Arm 2: PLC_PHYSICAL** Age at study entry, mean (SD) years: 58.4 (6) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: 49.7 Time since menopause at study entry, mean years: 8.7

Intervention(s)/control	**Arm 1: CO2_LASER** Microablative fractional CO2 laser (SmartXide2 V2LR,Monalisa Touch; DEKA) Treatment intensity: 3 treatments 1 month apart, starting at baseline visit **Arm 2: PLC_PHYSICAL** Sham fractional CO2 laser (SmartXide2 V2LR,Monalisa Touch; DEKA) - using non-ablative low dose (0.5W) Treatment intensity: 3 treatments 1 month apart, starting at baseline visit Treatment duration (weeks): 12 Lubricant/moisturizer permitted: No
Duration of follow-up	12 weeks
Sources of funding	Not Industry funded
Sample size	N randomised: 60 N completers: 58 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: CO2_LASER** N randomised: 30 N completers: 28 discontinuation due to adverse events: 0 discontinuation for any reason: 2 dyspareunia scale used: VAS scale (0-10;LB) dyspareunia baseline mean: 8.6 dyspareunia baseline SD: 1.5 dyspareunia endpoint mean: 2.6 dyspareunia endpoint SD: 2.6 dyspareunia change from baseline mean: -6 dyspareunia change from baseline SD: 2.6 dryness scale used: VAS scale (0-10;LB) dryness baseline mean: 8 dryness baseline SD: 1.7 dryness endpoint mean: 2.4

	dryness endpoint SD: 2.9 dryness change from baseline mean: -5.6 dryness change from baseline SD: 2.8 discomfort scale used: VAS scale (0-10;LB) discomfort baseline mean: 3.9 discomfort baseline SD: 3.1 discomfort endpoint mean: 1 discomfort endpoint SD: 2.1 discomfort change from baseline mean: -2.9 discomfort change from baseline SD: 2.8 dysuria scale used: VAS scale (0-10;LB) dysuria baseline mean: 1.6 dysuria baseline SD: 2.4 dysuria endpoint mean: 0.6 dysuria endpoint SD: 1.5 dysuria change from baseline mean: -0.9 dysuria change from baseline SD: 2.1 **Arm 2: PLC_PHYSICAL** N randomised: 30 N completers: 30 discontinuation due to adverse events: 0 discontinuation for any reason: 0 dyspareunia scale used: VAS scale (0-10;LB) dyspareunia baseline mean: 8.7 dyspareunia baseline SD: 1.4 dyspareunia endpoint mean: 7.6 dyspareunia endpoint SD: 1.9 dyspareunia change from baseline mean: -1.1 dyspareunia change from baseline SD: 1.8 dryness scale used: VAS scale (0-10;LB) dryness baseline mean: 7.5 dryness baseline SD: 1.9 dryness endpoint mean: 5.6 dryness endpoint SD: 2.9 dryness change from baseline mean: -1.9 dryness change from baseline SD: 2

	discomfort scale used: VAS scale (0-10;LB) discomfort baseline mean: 3.1 discomfort baseline SD: 3.2 discomfort endpoint mean: 1.8 discomfort endpoint SD: 2.6 discomfort change from baseline mean: -1.4 discomfort change from baseline SD: 1.9 dysuria scale used: VAS scale (0-10;LB) dysuria baseline mean: 0.9 dysuria baseline SD: 1.6 dysuria endpoint mean: 0.6 dysuria endpoint SD: 1.2 dysuria change from baseline mean: -0.3 dysuria change from baseline SD: 1.5

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no differences at baseline between groups.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Double blinded study with no deviations from the intended intervention apparent.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for at least 93% of participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Some outcome measures reported in the trial protocol were not reported.)*

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain due to some outcomes in the trial protocol not reported in the study.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Tanmahasamut, 2020**

Bibliographic Reference Tanmahasamut, Prasong; Jirasawas, Titima; Laiwejpithaya, Somsak; Areeswate, Chatchai; Dangrat, Chongdee; Silprasit, Kittayaporn; Effect of estradiol vaginal gel on vaginal atrophy in postmenopausal women: A randomized double-blind controlled trial.; The journal of obstetrics and gynaecology research; 2020; vol. 46 (no. 8); 1425-1435

3 **Study details**

Country/ies where study was carried out	Thailand
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Any post-menopausal vaginal symptoms Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Both uterus & no uterus Breast or gynae cancer history: None
Patient characteristics	**Arm 1: ESTRADIOL_GEL** Age at study entry, mean (SD) years: 54.9 (9.79) Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 5.5 **Arm 2: LUBRICANT** Age at study entry, mean (SD) years: 56.43 (4.47)

	Age at study entry, median (range) years: NR(NR-NR) Age at menopause, mean years: NR Time since menopause at study entry, mean years: 7
Intervention(s)/control	**Arm 1: ESTRADIOL_GEL** Estradiol in KY-jelly lubricant gel. 2 mL (25Âµg estradiol) applied intravaginally daily for 2 weeks, and two doses per week for the next 6 weeks. **Arm 2: LUBRICANT** KY-jelly lubricant/ 2 mL applied intravaginally daily for 2 weeks, and two doses per week for the next 6 weeks. Treatment duration (weeks): 8 Lubricant/moisturizer permitted: Yes in all treatment arms
Duration of follow-up	8 weeks
Sources of funding	Not Industry funded
Sample size	N randomised: 80 N completers: 75 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_GEL** N randomised: 40 N completers: 38 discontinuation due to adverse events: 0 discontinuation for any reason: 2 dyspareunia scale used: transfomred Thai-FSFI-pain domain dyspareunia baseline mean: 5.03 dyspareunia baseline SD: 4.32 dyspareunia endpoint mean: 0.58 dyspareunia endpoint SD: 5.62 dyspareunia change from baseline mean: -4.79 dyspareunia change from baseline SD: 4.65 dryness scale used: transfomred Thai-FSFI-lubrication domain dryness baseline mean: 3.76 dryness baseline SD: 4.66

	dryness endpoint mean: 2 dryness endpoint SD: 4.27 dryness change from baseline mean: -1.94 dryness change from baseline SD: 4.12 **Arm 2: LUBRICANT** N randomised: 40 N completers: 37 discontinuation due to adverse events: 0 discontinuation for any reason: 3 dyspareunia scale used: transfomred Thai-FSFI-pain domain dyspareunia baseline mean: 6.84 dyspareunia baseline SD: 3.38 dyspareunia endpoint mean: 4.48 dyspareunia endpoint SD: 5.94 dyspareunia change from baseline mean: -2.3 dyspareunia change from baseline SD: 5.07 dryness scale used: transfomred Thai-FSFI-lubrication domain dryness baseline mean: 4.48 dryness baseline SD: 4.95 dryness endpoint mean: 4.94 dryness endpoint SD: 5.16 dryness change from baseline mean: 0.57 dryness change from baseline SD: 5.12

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear if randomisation was concealed. No differences at baseline between groups.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Study was double blinded with no deviations from the intended interventions.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for 94% of participants.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measures used with assessors blinded to intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Study reported and analysed as reported in trial protocol.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns mainly due to insufficient information regarding concealment method.)*
Overall bias and directness	Overall directness	Directly applicable

1

2 **Weisberg, 2005**

Bibliographic Reference	Weisberg, E; Ayton, R; Darling, G; Farrell, E; Murkies, A; O'Neill, S; Kirkegard, Y; Fraser, I S; Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet; Climacteric; 2005; vol. 8 (no. 1); 83-92

3 **Study details**

Country/ies where study was carried out	Australia
Study type	Randomised controlled trial (RCT)
Inclusion / exclusion criteria	GU symptom inclusion criteria: Significant signs or symptoms of urogenital atrophy Scale used to assess GU symptom severity for trial entry: NR Uterus or not: Uterus

	Breast or gynae cancer history: NR
Patient characteristics	**Arm 1: ESTRADIOL_RING** Age at study entry, mean (SD) years: 58.1 (NR) Age at study entry, median (range) years: NR(46-81) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR **Arm 2: ESTRADIOL_TAB** Age at study entry, mean (SD) years: 57.5 (NR) Age at study entry, median (range) years: NR(46-72) Age at menopause, mean years: NR Time since menopause at study entry, mean years: NR
Intervention(s)/control	**Arm 1: ESTRADIOL_RING** Estring - vaginal ring containing 2mg micronized 17-beta-estradiol. Releases 8Âµg per 24hrs over 90 days. **Arm 2: ESTRADIOL_TAB** Vagifem - vaginal tablet 2Âµg micronized 17-beta-estradiol. Once daily for 2 weeks then twice per week. Treatment duration (weeks): 12 Lubricant/moisturizer permitted: NR
Duration of follow-up	12 weeks
Sources of funding	Industry funded
Sample size	N randomised: 185 N completers: 146 Analysis method: completers ITT imputation method: NR
Outcome data	**Arm 1: ESTRADIOL_RING** N randomised: 126 N completers: 94 discontinuation due to adverse events: 15 discontinuation for any reason: 32 **Arm 2: ESTRADIOL_TAB** N randomised: 59

	N completers: 52 discontinuation due to adverse events: 2 discontinuation for any reason: 7

Critical appraisal

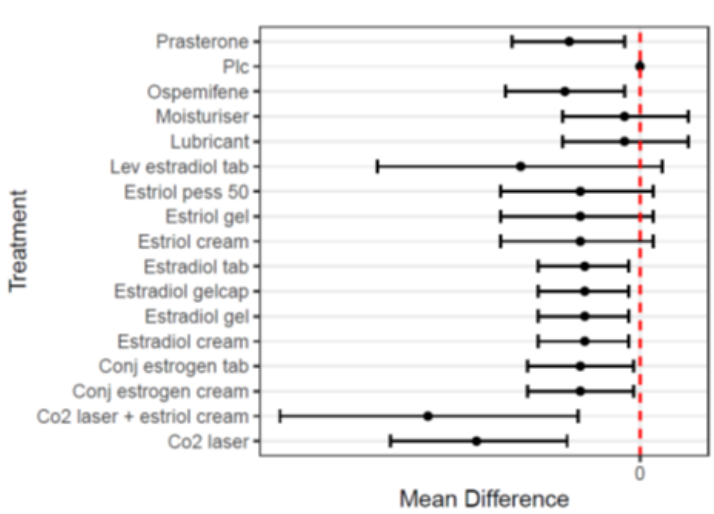
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation with no difference at baseline between groups.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Study was open labelled with insufficient information on analysis.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Larger dropout rate in ESTring group with dropouts due to adverse effects of ESTring. Completer analysis used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Outcome assessors were blinded to treatment condition.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available.)*
Overall bias and directness	Risk of bias judgement	High *(Study had high risk of bias in missing outcome data.)*
Overall bias and directness	Overall directness	Directly applicable

Appendix E Network meta-analysis forest plots

Forest plots for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

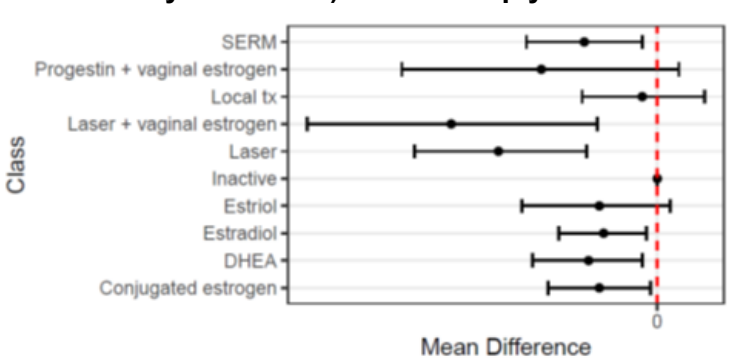
See Appendix L for NMA results including effects versus placebo and ranking tables.

Figure 6: Treatment level vulvovaginal dryness. Mean Differences (MD) and 95% credible intervals for every intervention compared to Placebo (reported on 4-point 0-3 dryness scale). MD < 0 imply a reduction in dryness compared to Placebo.



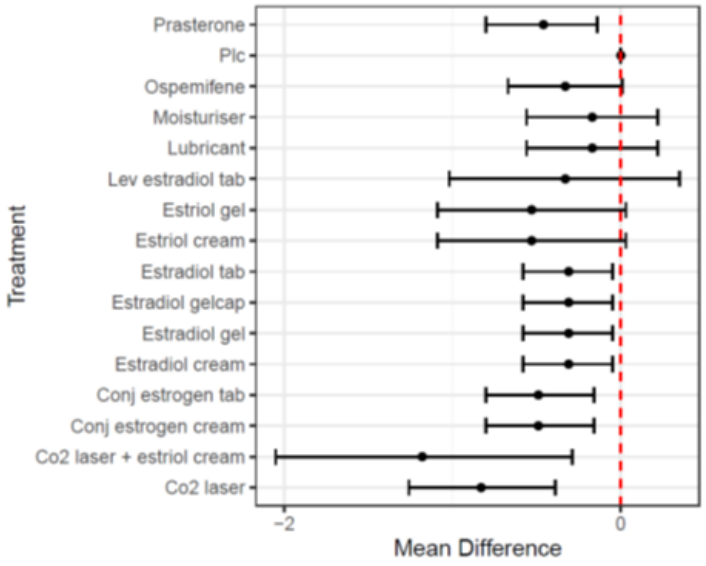
Mean Difference	95%CrI
−0.32	(−0.58, −0.07)
0.00	Reference
−0.34	(−0.61, −0.07)
−0.07	(−0.35, 0.22)
−0.07	(−0.35, 0.22)
−0.54	(−1.19, 0.1)
−0.27	(−0.63, 0.06)
−0.27	(−0.63, 0.06)
−0.27	(−0.63, 0.06)
−0.25	(−0.46, −0.05)
−0.25	(−0.46, −0.05)
−0.25	(−0.46, −0.05)
−0.25	(−0.46, −0.05)
−0.27	(−0.51, −0.03)
−0.27	(−0.51, −0.03)
−0.96	(−1.63, −0.28)
−0.74	(−1.13, −0.33)

Figure 7: Class level vulvovaginal dryness. Mean Differences (MD) and 95% credible intervals for every class compared to Inactive (reported on 4-point 0-3 dryness scale). MD < 0 imply a reduction in dryness compared to Inactive.



Mean Difference	95%CrI
−0.34	(−0.61, −0.07)
−0.54	(−1.19, 0.1)
−0.07	(−0.35, 0.22)
−0.96	(−1.63, −0.28)
−0.74	(−1.13, −0.33)
0.00	Reference
−0.27	(−0.63, 0.06)
−0.25	(−0.46, −0.05)
−0.32	(−0.58, −0.07)
−0.27	(−0.51, −0.03)

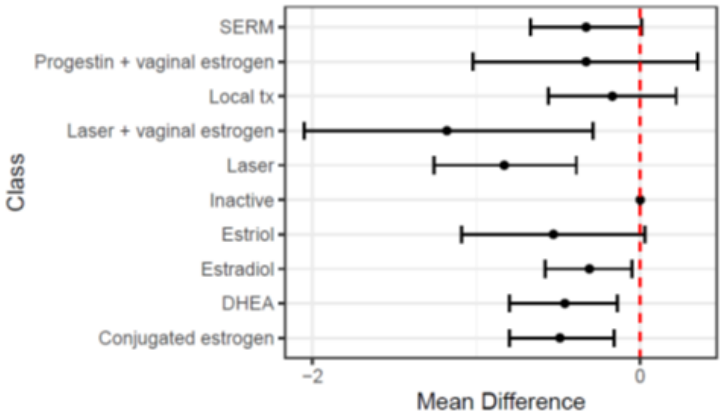
Figure 8: Treatment level pain with sex (dyspareunia). Mean Differences (MD) and 95% credible intervals for every intervention compared to Placebo (reported on 4-point 0-3 dyspareunia scale). MD < 0 imply a reduction in dyspareunia compared to Placebo.



Mean Difference	95%CrI
−0.46	(−0.8, −0.14)
0.00	Reference
−0.33	(−0.67, 0.01)
−0.17	(−0.56, 0.22)
−0.17	(−0.56, 0.22)
−0.33	(−1.02, 0.35)
−0.53	(−1.09, 0.03)
−0.53	(−1.09, 0.03)
−0.31	(−0.58, −0.05)
−0.31	(−0.58, −0.05)
−0.31	(−0.58, −0.05)
−0.31	(−0.58, −0.05)
−0.49	(−0.8, −0.16)
−0.49	(−0.8, −0.16)
−1.18	(−2.05, −0.29)
−0.83	(−1.26, −0.39)

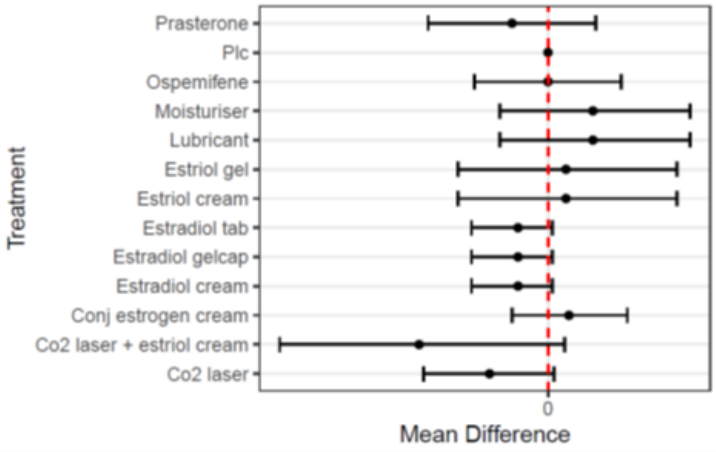
1

Figure 9: Class level pain with sex (dyspareunia). Mean Differences (MD) and 95% credible intervals for every class compared to Inactive (reported on 4-point 0-3 dyspareunia scale). MD < 0 imply a reduction in dyspareunia compared to Inactive.



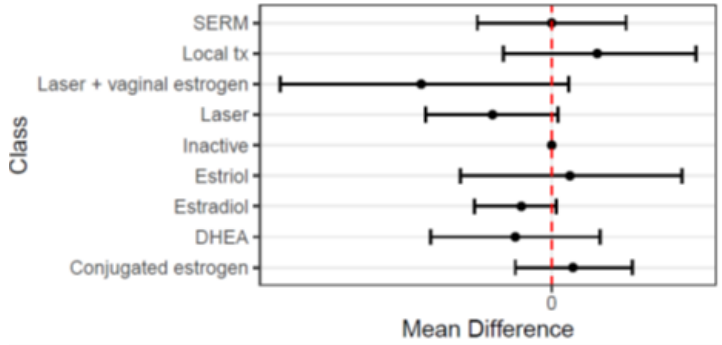
Mean Difference	95%CrI
−0.33	(−0.67, 0.01)
−0.33	(−1.02, 0.35)
−0.17	(−0.56, 0.22)
−1.18	(−2.05, −0.29)
−0.83	(−1.26, −0.39)
0.00	Reference
−0.53	(−1.09, 0.03)
−0.31	(−0.58, −0.05)
−0.46	(−0.8, −0.14)
−0.49	(−0.8, −0.16)

Figure 10: Treatment level vulvovaginal discomfort/irritation. Mean Differences (MD) and 95% credible intervals for every intervention compared to Placebo (reported on 4-point 0-3 discomfort scale). MD < 0 imply a reduction in discomfort compared to Placebo.



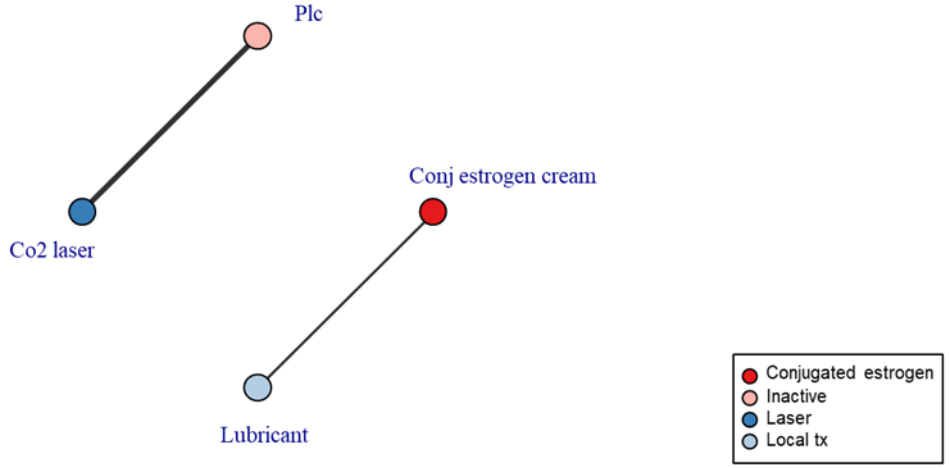
Mean Difference	95%CrI
−0.24	(−0.8, 0.32)
0.00	Reference
0.00	(−0.49, 0.49)
0.30	(−0.32, 0.95)
0.30	(−0.32, 0.95)
0.12	(−0.6, 0.86)
0.12	(−0.6, 0.86)
−0.20	(−0.51, 0.03)
−0.20	(−0.51, 0.03)
−0.20	(−0.51, 0.03)
0.14	(−0.24, 0.53)
−0.86	(−1.79, 0.11)
−0.39	(−0.83, 0.04)

Figure 11: Class level vulvovaginal discomfort/irritation. Mean Differences (MD) and 95% credible intervals for every class compared to Inactive (reported on 4-point 0-3 discomfort scale). MD < 0 imply a reduction in discomfort compared to Inactive.



Mean Difference	95%CrI
0.00	(−0.49, 0.49)
0.30	(−0.32, 0.95)
−0.86	(−1.79, 0.11)
−0.39	(−0.83, 0.04)
0.00	Reference
0.12	(−0.6, 0.86)
−0.20	(−0.51, 0.03)
−0.24	(−0.8, 0.32)
0.14	(−0.24, 0.53)

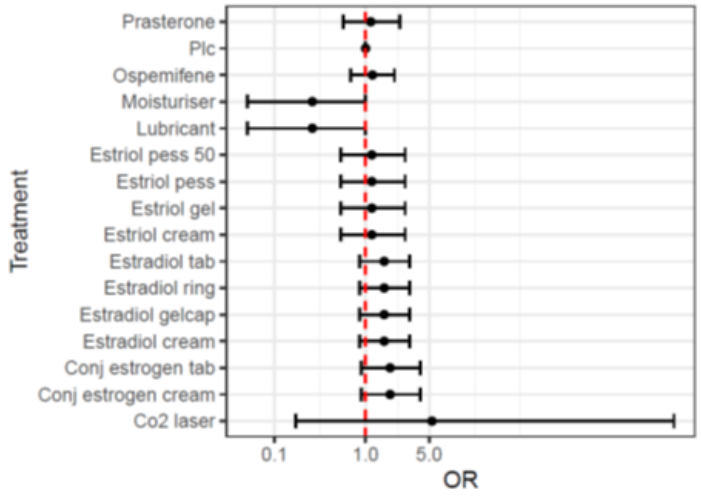
Figure 12: Network diagram of all studies included in analysis by intervention. Pain/discomfort when urinating (dysuria).



Plc: Placebo

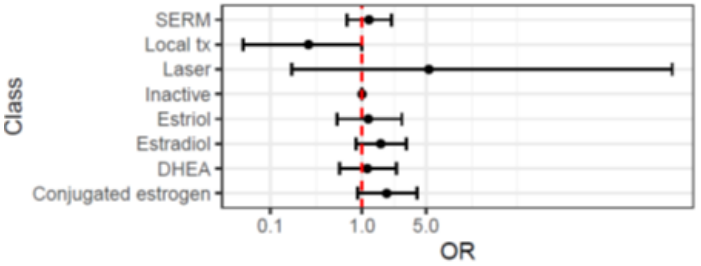
Note: This figure was generated to explain that an NMA was not possible for this outcome because the network is disconnected. The committee did not use this evidence in pairwise analysis for decision making. This is supplementary to the main analysis and is included here for completeness.

Figure 13: Treatment level discontinuation due to adverse events. Odds Ratios (OR) and 95% credible intervals for every intervention compared to Placebo for discontinuation due to adverse events. OR > 1 imply a reduction in discontinuation due to adverse events compared to Placebo.



OR	95%CrI
1.14	(0.57, 2.36)
1.00	Reference
1.19	(0.68, 2.08)
0.26	(0.05, 1)
0.26	(0.05, 1)
1.17	(0.53, 2.72)
1.17	(0.53, 2.72)
1.17	(0.53, 2.72)
1.17	(0.53, 2.72)
1.60	(0.86, 3.03)
1.60	(0.86, 3.03)
1.60	(0.86, 3.03)
1.60	(0.86, 3.03)
1.86	(0.89, 4.01)
1.86	(0.89, 4.01)
5.37	(0.17, 2440.6)

Figure 14: Class level discontinuation due to adverse events. Odds Ratios (OR) and 95% credible intervals for every class compared to Inactive for discontinuation due to adverse events. OR > 1 imply a reduction in discontinuation due to adverse events compared to Inactive.



OR	95%CrI
1.19	(0.68, 2.08)
0.26	(0.05, 1)
5.37	(0.17, 2440.6)
1.00	Reference
1.17	(0.53, 2.72)
1.60	(0.86, 3.03)
1.14	(0.57, 2.36)
1.86	(0.89, 4.01)

Appendix F GRADE and tables

GRADE tables for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

GRADE was not undertaken for this review question. Instead, changes in the effectiveness evidence for the interventions of most interest in the NMA were explored during sensitivity analysis in the bespoke economic model based on the NMA. Methods and results of the sensitivity analysis are presented in Appendix I.

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for further information.

Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Table 15: Economic evidence tables for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: NICE 2023 **Country**: UK **Type of economic analysis:** Cost utility **Source of funding:** Department of Health and Social Care for England	**Intervention:** 1) Estriol 2) Estradiol 3) Prasterone 4) Ospemifene 5) Laser Interventions included non-hormonal moisturisers and lubricants for ospemifene and laser **Comparator:** Non-hormonal moisturisers and lubricants	**Population:** Hypothetical cohort of women with bothersome genitourinary symptoms associated with the menopause **Modelling approach**: Markov model **Source of baseline data:** Two RCTs (as reported in Dymond 2021) set in the US of 826 an 919 women investigating the efficacy, safety and tolerability of ospemifene for treating VVA in post-menopausal women. **Source of effectiveness data:** Accompanyin	**Mean cost per participant:** Intervention: 1)£95.25 2)£110.26 3)£133.97 4)£458.60 5)£2,825.82 Comparator: £98.51 Difference (vs comparator): 1)-£3.26 2)£11.75 3)£35.46 4)£360.08 5)£2,727.31 **Mean outcome per participant (QALYs):** 1)0.7653 2)0.7547 3)0.7621 4)0.7562 5)0.7802 Comparator: 0.7482 Difference (vs comparator): 1)0.0171	**INMB (£20k per QALY vs comparator):** 1)£345.51 2)£119.80 3)£242.87 4)-£200.09 5)-£2,086.52 **Probability of being cost effective:** **£20k Threshold per QALY**: Estriol 60.0% Prasterone: 31.4% Estradiol 7.0% All other interventions had a probability less than 1% **Sensitivity analysis:** Estriol remained the most cost effective option in all but 3 of the deterministic sensitivity analyses.	**Perspective:** UK NHS & PSS **Currency**: UK Sterling (£) **Cost year**: 2020/21 **Time horizon**: 1 year, sensitivity analysis to 10 years **Discounting**: 3.5% per annum QALYs and Costs **Applicability**: Directly applicable **Limitations**: Minor limitations **Other comments**: Bespoke economic model to inform this guideline

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		g NMA of RCTs **Source of utility data:** Health state utilities were sourced from DiBonaventura 2015. **Source of cost data:** GP appointment costs and gynaecologist costs were take from PSSRU and NHS Cost Collection respectively. Laser costs were estimated from the median of costs from private centres and committee estimate.	2)0.0066 3)0.0139 4)0.0080 5)0.0320	Laser was the preferred option when a 10 year time horizon with continued effect was assumed and prasterone was the preferred option when only interventions for those contraindicated for oestrogen were considered.	
Author and year: Dymond 2021 **Country**: UK (Scotland) **Type of economic analysis:** Cost utility **Source of funding:** Shionogi Limited, UK	**Intervention:** Ospemifene 60mg once daily plus non-hormonal moisturisers and lubricants **Comparator:** Non-hormonal moisturisers and lubricants	**Population**: Hypothetical cohort of women with vulvovaginal atrophy for which local oestrogens contraindicated and self reported moderate or severe symptoms on the menopause rating scale. **Modelling approach**: Markov model **Source of**	**Mean cost per participant:** Intervention: £6,766 Comparator: £5,918 Difference: £847 **Mean outcome per participant (QALYs):** Intervention: 12.05 Comparator: 11.99 Difference: 0.06	**ICER (per QALY gained):** £14,138 **Probability of being cost effective:** **£20k Threshold per QALY**: 89% **Sensitivity analysis:** Deterministic sensitivity analysis undertaken around nearly all inputs and alternative assumptions around the	**Perspective:** UK NHS & PSS (Scotland) **Currency**: UK Sterling (£) **Cost year**: 2017/18 **Time horizon**: Lifetime **Discounting**: 3.5% per annum QALYs and Costs **Applicability**: Directly applicable **Limitations**: Potentially serious

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		baseline data: Two RCTS (Bachmann 2010) set in the US of 826 an 919 women investigating the efficacy, safety and tolerability of ospemifene for treating VVA in post-menopausal women. **Source of effectiveness data:** As for baseline **Source of utility data:** Health state utilities were sourced from DiBonaventura 2015. Adverse event disutilities were based on previous NICE guidelines and assumption. **Source of cost data:** Cost of ospemifene was taken from BNF with cost of moisturiser/lubricant from Scottish Dispensing data. GP costs from PSSRU and gynaecology outpatient visits from ISD Scotland cost book. Adverse event costs		longevity of effectiveness and a shortened time horizon. All sensitivity analyses still favoured ospemifene at a threshold of £20k per QALY	limitations **Other comments**: Funded by the manufacturer of ospemifene

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		were a mix of PSSRU, Scottish dispensing data and assumption			

BNF: British National Formulary; GP: General practitioner; ICER: Incremental Cost Effectiveness Ratio; ISD: Information Service Division; PSSRU: Personal Social Services Research Unit; QALY: Quality Adjusted Life Year; RCT: Randomised Controlled Trial: VVA: Vulvovaginal Atrophy; Vs: Versus

Appendix I Economic model

Economic model for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Background

Moisturisers, lubricants and oestrogen based treatments such as oestradiol are established as standard of care for genitourinary symptoms associated with the menopause. Other treatments are available but are associated with higher costs but may provide improved outcomes or be available to a larger population for example people contraindicated or otherwise not suitable for oestrogen based treatments. This cost utility analysis aims to compare the cost effectiveness of established and newer treatments compared to non-hormonal moisturiser and lubricants.

Methods

Aim of analysis

The aim of the analysis was to estimate the cost utility of interventions for the treatment of troublesome genitourinary symptoms associated with the menopause.

Population

The population considered by this economic model were treatment naïve women, non-binary and trans people with troublesome genitourinary symptoms associated with the menopause. As the pathway for the model starts with a GP appointment it was considered that all people would have severe enough symptoms to have made this contact. It was assumed that all people in the model were clinically suitable for all interventions and were physically able to receive and apply them except for those that have to be administered by a trained clinician. Although the age of the population did not feed directly into the economic model it was assumed the average age of the cohort was 62 years in line with the cohort used to inform the quality-of-life parameters (DiBonaventura 2015).

Interventions considered by the economic model

The network meta-analysis (NMA) which accompanies this model identified randomised controlled trials (RCTs) covering 17 different interventions which were covered by 10 broader classes. As the results of the NMA did not find any evidence of differences by intervention within these classes this economic model only considers interventions at the class level.

Classes of interventions that the committee thought were not plausible treatment options for this patient group were excluded from the economic model even where evidence was found for them in the NMA. Placebo and conjugated oestrogen were excluded for this reason. The committee highlighted it would not be ethical to prescribe placebo when there are other effective treatments available. Conjugated oestrogen was excluded because it is not widely available within the UK. Combination therapies laser + vaginal oestrogen and progestin + vaginal oestrogen were not considered in the economic model as they had limited evidence within the NMA and consequently imprecise estimates of effectiveness. Such combinations

are also not commonly prescribed within the NHS and the level of clinical evidence was unlikely to change this.

The interventions included in the economic model are listed in Table 16. Some interventions have been given alternative labels to the labels of classes in the accompanying NMA either because a class only contains one intervention, an intervention within the class is the one overwhelming used within the UK or where a different class name will make it clearer what is considered by the economic model.

Table 16: Interventions considered in the economic evaluation and their corresponding class label in the network meta-analysis

Intervention in economic model	Class label in network meta-analysis
(Non-hormonal) moisturisers and lubricants	Local treatment
Prasterone	Dehydroepiandrosterone (DHEA)
Laser	Laser
Ospemifene	Selective estrogen receptor modulator (SERM)
Estriol	Estriol
Estradiol	Estradiol

The NMA assumed additivity of non-hormonal moisturiser/lubricant when given alongside other treatments in trials such that the effect of the non-hormonal moisturiser/lubricant in both arms would cancel out. To be consistent with this assumption in the economic model it was assumed that people receiving laser and ospemifene would also receive non-hormonal lubricant/moisturiser. This assumption was not applied to other interventions as it was considered that the treatment would have both an active ingredient component (for example oestrogen) and a lubricating or moisturising component. It was also the committees clinical experience that lubricants/moisturisers would not be recommended alongside these interventions. This was also supported by the protocols of the RCTs included in the NMA which largely did not allow the use of lubricant/moisturiser in interventions which were not laser or ospemifene.

Model structure

A Markov model was constructed representing a cohort of women, non-binary and trans people to estimate the cost utility of the interventions of interest compared to non-hormonal moisturiser or lubricant. The Markov component of the models had three health states based on the Menopause Rating Scale (MRS) (Heinemann 2003) which mirrors the 0-3, least best scale from the accompanying NMA results. These health states were none (0), mild (1) and a combined moderate/severe (2-3). The aim of treatment was to move people from moderate/severe symptoms to none or mild symptoms and that reducing symptoms from severe to moderate would likely be seen as a treatment failure. There was also great variation between the studies that used the MRS and were included in NMA of the proportion of those starting with moderate and severe symptoms. Moderate and severe symptoms would also allow all interventions within the economic model to be used inline with their licensed indication. Having 1 health state for all moderate and severe symptoms would capture the severity of symptoms for the majority of people in the included RCTs and make estimates of effectiveness more applicable to the model population. The menopause rating scale is discussed in more detail below.

All people are in the moderate/severe state at the commencement of the model. Over 12 weeks, the most commonly reported follow-up time in the included RCTs, people will either remain in the moderate/severe health state or transition to the none or mild health states based on the effectiveness estimates of the treatment received. Costs and quality adjusted life years (QALYs) will be calculated, as discussed below, dependent on time spent in each state. The Markov model only had one 12-week cycle but this was extrapolated to 1 year in the base-case and up to 10 years in sensitivity analysis. The study took a UK NHS and PSS perspective in line with the NICE guidelines manual. (NICE 2014) The committee highlighted there were likely to be wider societal costs through time off work as a result of genitourinary symptoms associated with the menopause. There was also likely to be out of pocket costs for women who buy their own medication, pain relief and other interventions over the counter. Whilst we did not formally estimate these costs, we do consider these issues in the discussion section of this report.

Discounting

The base case analysis had a time horizon of 1 year and neither costs or QALYs were discounted for this analysis. In sensitivity analyses where the time horizon exceeded 1 year all costs and QALYs were discounted at 3.5% per annum in line with the NICE Guidelines Manual (NICE 2014).

Model inputs

Effectiveness

Effectiveness was almost exclusively based on the results of the accompanying NMA. Only two outcomes from the NMA fed directly into the economic model, vulvovaginal dryness and dyspareunia. These were considered the two outcome which would have the largest impact on quality of life and the outcome was reported in at least 1 RCT for all interventions in the economic model and therefore the NMA could estimate effectiveness. Dysuria was only reported for a limited number of classes in the NMA, of which only laser was considered by this economic analysis. Discomfort was estimated for all interventions in this economic analysis but overall participants from relevant RCT arms were much fewer than for the other outcomes. The committee also hypothesised that discomfort would overlap and correlate significantly with the dryness and dyspareunia outcomes and its inclusion in the economic model would lead to an overestimate of the impact on quality of life.

The back-converted estimates on the 0-3 scale (least best) from the accompanying NMA were used to estimate transition probabilities for the model. These were converted using evidence from the Bachmann 2010 RCT a study included in the accompanying NMA. Bachmann 2010 was an RCT comparing placebo plus lubricant to ospemifene plus lubricant in 544 people with at least 1 moderate or severe symptom of vulvovaginal atrophy, 464 of whom completed the study period. Given the additive assumption used in the NMA and economic model these map to interventions moisturiser/lubricant and ospemifene respectively in this economic evaluation. Full discussion of the study characteristics are presented in the clinical evidence report. Bachmann reported changes in dryness and dyspareunia in the RCT on the 0-3 scale, least best as discussed for both interventions. The Bachmann 2010 RCT also collected MRS state at baseline and 12 weeks after the interventions and reported in Dymond 2021. These results are reported in Table 19.

From the reported MRS states in Bachmann 2010 a proportion could be calculated for people moving from the moderate/severe state to both the none state and mild state at 12 weeks from the start of treatment. For ospemifene this was 35.2% moving to none and 26.3% for mild. The corresponding values for moisturiser/lubricant were 25.5% and 20.3% respectively. Probability of remaining in the moderate/severe state was equal to these proportions subtracted from 1.

It was assumed that changes on the 0-3 scale for dryness and dyspareunia would have a linear relationship with the probability of transitioning between states. Based on this assumption, simultaneous equations could be formed and solved to estimate the coefficient to allow changes on the scale to be converted to transition probabilities. The simultaneous equations were formulated as:

$$Moisturiser/Lubricant: \alpha(\text{change in dyspareunia}) + \beta(\text{change in dryness}) = p(\text{transition}_{Mild})$$

$$Ospemifene: \alpha(\text{change in dyspareunia}) + \beta(\text{change in dryness}) = p(\text{transition}_{Mild})$$

Where change in dyspareunia and change in dryness are the changes from baseline on the 0-3 scale, least best in the Bachmann trial and $p(\text{transition}_{Mild})$ is the probability of transitioning to the mild state from the moderate/severe state for moisturiser/lubricant and ospemifene respectively.

These can then be solved to find coefficients α and β. The same was also done but to estimate the transition from moderate/severe state to none state:

$$Moisturiser/Lubricant: \alpha(\text{change in dyspareunia}) + \beta(\text{change in dryness}) = p(\text{transition}_{None})$$

$$Moisturiser/Lubricant: \alpha(\text{change in dyspareunia}) + \beta(\text{change in dryness}) = p(\text{transition}_{None})$$

$$Ospemifene: \alpha(\text{change in dyspareunia}) + \beta(\text{change in dryness}) = p(\text{transition}_{None})$$

From this we estimated 4 sets of coefficients to be applied to the outcomes of the 0-3 scale from the NMA to give transition probabilities for all interventions considered. For estimating the transition probabilities moisturiser/lubricant and ospemifene estimates from the NMA were used rather than those estimated in Bachmann 2010. Therefore, the transition probabilities for these outcomes in the model differ to those reported above. All estimated coefficients and transition probabilities are presented in Table 19.

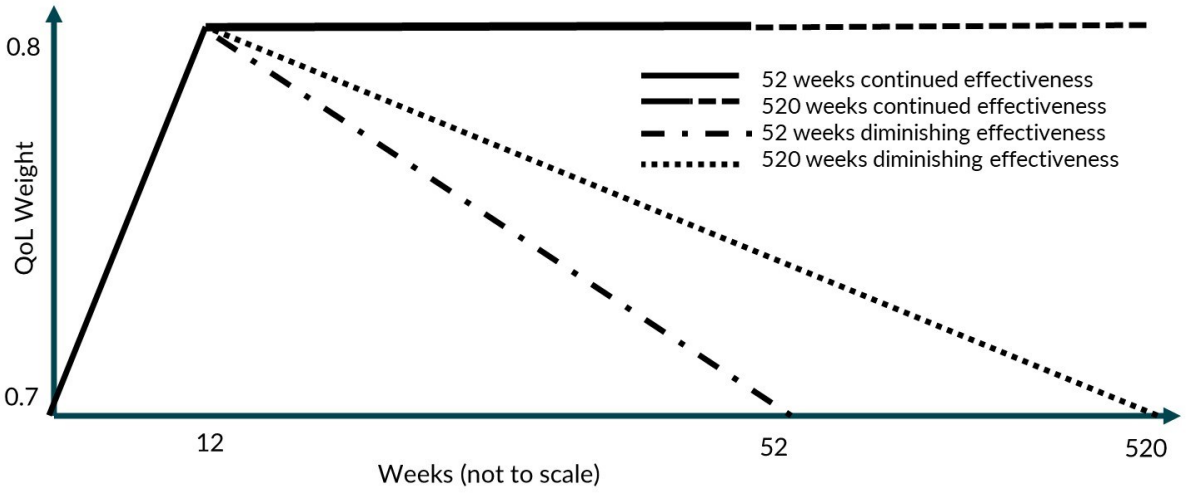
For all analyses where an intervention is effective it is assumed that the increase in quality of life happens at a constant rate from the baseline value to the estimated health state utility at 12 weeks. This is shown diagrammatically in Figure 15.

Continuation of effectiveness after 12 weeks

In the base-case analysis it was assumed that the difference in effectiveness between the intervention and the comparator remained constant from 12 weeks until 52 weeks the time horizon of the base-case model. An alternative assumption was made during sensitivity analysis that the effectiveness would return to the baseline value at a constant rate over the time horizon of the model.

Both the assumptions above were replicated when the time horizon was extended to 10 years. These assumptions are presented in Figure 15.

Figure 15: Continuation of effectiveness assumptions used in the economic model



Discontinuation and adverse events

Costs and QALYs associated with discontinuation (for either lack of efficacy or intolerable adverse events) or adverse events as a direct result of treatment were not included in the economic model.

Evidence around discontinuation was sparse in the accompanying NMA. There was only strong evidence that discontinuation was lower in moisturiser or lubricant than for other treatments considered in the economic model. Estimates for all other interventions considered by this economic model had increased odds of discontinuation compared to lubricant or moisturiser although the 95% credible intervals overlapped for all interventions. This was in line with the expectations of the guideline committee who thought adverse events for lubricants and moisturisers would be far less than for treatments with hormonal components, ospemifene or lasers. Given there was no strong evidence of different odds of discontinuation due to adverse events for treatments which were not lubricants or moisturisers this parameter was not included in the economic model. The committee acknowledged that excluding this parameter would bias against moisturiser and lubricant.

The economic model also did not include adverse events. The evidence used to inform the NMA did not identify any major adverse events which were likely to have a very large impact on either costs or quality of life. All adverse events identified were relatively minor, non-permanent and could be effectively treated over a short period of time either through relatively inexpensive treatments or discontinuation. Dymond 2021 estimated that adverse event costs, including additional clinical contact time, accounted for less than 1% of the total costs in their economic model comparing ospemifene to moisturiser in a similar population who were not suitable for local vaginal oestrogen. Most of those costs being for treating urinary tract infections (UTI) or vaginal myocital infection (VMI) both of which are treated with

inexpensive antibiotics given via tablet, creams or gels. Dymond 2021 also estimated very small quality of life detriments associated with these 2 events. UTI had a utility detriment of 0.19 with an average duration of 4.2 days and VMI had a detriment of 0.25 and average duration of 3 days. These account for less than a percentage point of the utility of a woman with GU symptoms associated with the menopause. (see section on quality of life). Dymond 2021 also estimated a utility detriment of 0.02 for hot flushes with an average duration of 2 minutes. No costs were assigned to this outcome in Dymond. These events also estimated by Dymond 2021 to impact less than 10% of the model population.

Based on the very small impact on both costs and QALYs from adverse events associated with the interventions considered and the uncertainty around difference in discontinuation for interventions other than moisturiser and lubricant no costs or changes in QALY were assigned to them in the economic model. Whilst adverse events were not seen as economically important they will be important for people receiving these treatments and they should be fully explained so that informed decision making can take place.

Survival

The accompanying clinical evidence review did not consider survival and it was the opinion of the committee that there would be no difference in survival between the different interventions considered by this economic evaluation. In all interventions there is always a probability of death that is not directly related either to the treatment (treatment related mortality) or the condition being considered (disease related mortality). It was not expected that survival for the population undergoing these treatments would be different to that of the age-matched general population. Probabilities of mortality within the next year and 10 years (the 2 time-horizons considered in this report) are calculated from female National Life Tables reported in Office of National Statistics (ONS) Life Tables. Mortality relevant to our model is reported in Table 17.

Table 17: Estimated mortality for model population

Age at start of model (years)	Probability death within 1 year
60	0.52%
62 (assumed age of model cohort)	0.64%
65	0.81%
70	1.29%

Given that the probabilities for mortality did not differ between groups and they were less than 1% for ages similar to that assumed for the cohort, mortality was not modelled in the economic evaluation as it would be very unlikely to change any conclusions. The values were also not adjusted for the excess deaths from COVID-19 for the mid-year estimates for 2020. These estimates may therefore represent an overestimate of the probability of mortality.

Quality of life

Utility weights were taken from DiBonaventura 2015. The study used data from the International Women's Health Study, an internet survey of postmenopausal women between the ages of 40 and 75 in Europe and the United States. The cross-sectional survey had just over 7000 responders with a subset of 1096 from the United Kingdom (UK) being used to

inform the utility weights for quality-of-life in this model. Women from the UK subset had a mean age of 62 years. Quality-of-life was assessed using the EQ-5D-3L. Responses were converted into health utility scores using the UK general population value set. This is congruent to NICE's preferred methods of measuring health related quality of life for economic evaluations. (NICE 2014) Adjusted values reported by the study authors were used. These adjusted for differences in age, marital status, income, education, frequency of exercise, smoking behaviour, alcohol intake, body mass index and comorbidities.

Patients also self-assessed their symptom severity of the menopause rating scale (MRS). This is a widely used instrument for measuring symptom severity and has been validated in a wide range of areas where symptoms associated with the menopause are relevant. (Heinemann 2003) The scale measures self-perceived subjective symptom severity on a scale of 0 to 4 representing none, mild, moderate, severe and extremely severe with a lower score representing less severe symptoms. As has been done in previous research the severe and extremely severe states have been combined given the relative rarity of extremely severe symptoms. This gives a 0-3 scale with lower score being better which is comparable to the 0-3 scale results which has been back-converted from the NMA and used for the health states in this economic model. EQ-5D health utility scores were than presented on this scale.

The authors estimated health utilities of between 0.68 for those with severe symptoms up to 0.82 for no symptoms. As discussed above the moderate and severe states were combined for the purposes of economic modelling using the proportions for each state from Bachmann 2010. This gave a weighted health utility score of 0.71 for the moderate/severe health state. As it was assumed that all people in the model cohort had moderate or severe symptoms at the start this also represented the baseline health utility score at the start of the commencement of the model. As the baseline estimate did not feed into the incremental analysis this was not varied during sensitivity analyses. As the health states for which health utilities were estimated and those used in the model were both from the MRS and were considered comparable health utility estimates were applied directly to the proportion and time the model cohort spent in each health state. All health states and confidence intervals are reported in Table 19.

Health utility data from the RCTs considered in the NMA were also investigated to see their suitability for informing the economic model. From this, 23 RCTs were identified which reported quality of life data. The majority of these used disease specific measures most frequently the Female Sexual Function Index (FSFI), Day to Day Impact of Vaginal Aging (DIVA) Questionnaire and Menopause-specific Quality of Life (MENQOL) Questionairre. A few studies used generic measures such as the 36 Item Short Form Survey (SF-36) and visual analogue scales. No studies included in the NMA measured quality-of-life on the EQ-5D. Given the samples for all these studies were smaller than DiBonaventura 2015, covered a limited number of interventions, were not all scored using general population tariffs and did not use NICE's preferred measure of quality of life these values were not used in the economic model.

Costs and resource use

Clinical contact

The cost of a 1 face-to-face GP appointment was taken from Personal Social Services Research Unit (PSSRU) costs of health and social care (Jones 2022). Jones 2022 estimated a cost per GP appointment, assuming an average time of 9.22 minutes, of £36. This included direct staff costs (from employing a practice nurse for example) but did not include costs associated with education and training required to become a GP (qualification costs).

The cost of a telephone appointment was also taken from PSSRU and estimated a cost per appointment of £15.80. This cost included both direct staff costs and qualification costs. Jones estimated qualification costs at £45,998 per year and assumed telephone appointments would run 2002 hours per year with an average 4 minutes per consultation. Qualification costs therefore work at £22.97 per hour or £1.53 per appointment. This was subtracted from the Jones 2022 estimate to give a cost per telephone appointment of £14.27.

The costs for a gynaecologist appointment were taken from NHS National Cost Collection 2021/22. A non-admitted, first face-to-face appointment with a consultant (cost code WF01B) and subsequent face-to-face follow-up appointments (cost code WF01A) and were £244.60 and £196.09 respectively.

It was assumed that all people with troublesome genitourinary symptoms would initially attend 1 face-to-face GP appointment. For laser and ospemifene, which are more specialist interventions, it was also assumed that an appointment with a consultant gynaecologist would be needed prior to starting treatment. It was assumed there would be one annual follow-up meeting with the GP or consultant gynaecologist (for laser and ospemifene) per year. For those in whom genitourinary symptoms persisted at either a moderate or severe level it was assumed that they would attend 1 additional annual face-to-face meeting with a GP. The committee highlighted, from their own experience, that this may underestimate the amount of contact with healthcare professionals that those with moderate or severe symptoms would seek and therefore the impact on a great number of annual appointments was investigated during sensitivity analysis. A further sensitivity analysis was also undertaken to assume that all follow-up appointments associated with the initial treatment would be via telephone rather than face-to-face.

How laser and ospemifene would fit into a treatment pathway within the NHS were unclear. It was discussed that such interventions could potentially be prescribed by GPs with special interest in menopause as well as GPs more generally. This would reduce the need for a consultant gynaecologist before starting treatment. The assumption of needing a gynaecologist visit before starting laser and ospemifene was therefore removed during deterministic sensitivity analysis.

Cost of intervention

For all pharmacological interventions resource use and prices were estimated from the BNF (reference) as of March 2023. For some classes there were multiple interventions identified within them and within intervention of the NMA there were often alternative methods of application (tablet, gel, pessary etc) as well as different brands of drugs. Where this was the case, the committee used their expertise to identify the most applicable or common intervention for the NHS setting. If there were multiple interventions or preparations within in a class which were identified as applicable the least costly, based on NHS indicative prices

reported in the BNF was used. The cost of the intervention was only included in the model over the length of treatment course stated in the BNF.

For non-hormonal moisturisers and lubricants no prices were reported in the BNF and therefore the NHS drug tariff was used to estimate costs instead. As the NHS Drug Tariff reported multiple costs, the same process as for interventions in the BNF was used to identify the most suitable one.

For laser, no sources of cost were identified which estimated the cost from an NHS+PSS perspective. A range of prices were therefore obtained from the provision of laser in the private sector as well as an estimate from the guideline committee. The median value of this was used for the estimate of cost in the economic model. The costings assumed that treatment would be completed after 3 rounds the most common treatment regimen identified in the RCTs informing the NMA and the exclusive regimen for laser treatments costed from the private sector. From personal communications we identified three costs for laser treatment of £1,500, £1,990 and £3,600. Independent of this the committee estimated a cost of laser treatment of £3,000. A median value for laser treatment of £2,495 was estimated for the model. This median value was given a triangular distribution with an upper and lower limit of the range identified during PSA.

The preparation used for estimating costs and the treatment regimen from the BNF are presented in Table 18. Treatment was assumed to end after the indicated course but effectiveness would remain in line with the assumptions made above. Given the additive assumptions made in the NMA and this economic evaluation the cost of moisturiser/lubricant was also added to laser and ospemifene. It was assumed that the treatment regimen for moisturiser/lubricant would be identical whether used in addition to another treatment or by itself.

Table 18: Treatment regimens used to estimate costs in the economic model

Intervention	Treatment regimen	Brand name	NHS indicative cost
Moisturiser / lubricant	When needed. Assumed one 75ml needed for 12 week treatment course	YES WB water-based vaginal lubricant	£7.00 per 75ml tube
Prasterone	6.5mg daily	Intrarosa	£15.94 per 28 6.5mg tablets
Laser	3 courses of laser treatment	N/A	£2,495 per 3 courses
Ospemifene	60mg daily	Senshio	£39.50 per 28 60mg tablets
Estriol	1 applicatorful daily for 3-4 weeks, 1 applicatorful twice weekly	Ovestin	£4.45 per 15g of cream
Estradiol	Daily two weeks, twice weekly after two weeks	Multiple used for NHS indicative price	£15.00 per 24 10mg pessary

Over-the-counter medicines

Both non-hormonal moisturisers/lubricants and oestradiol can be purchased over the counter and this is a popular way of obtaining these interventions. This is especially the case where

the prescription charge is similar or higher than the over the counter cost such as for moisturiser/lubricant. When this happens the treatment costs are not incurred by the NHS. To reflect that people may prefer to purchase interventions this way a sensitivity analysis was undertaken where these interventions were given a zero cost in the analysis reflecting the zero cost under a NHS+PSS perspective. It was assumed that an individual would still make a GP appointment prior to this and thus this cost remained during this analysis. Where non-hormonal moisturiser/lubricant is used as an additional treatment it is also costed as zero in this analysis.

Laser is not widely available, if at all, for the treatment of genitourinary symptoms associated with the menopause in the NHS setting. Currently the vast majority of people undergoing this treatment do so in a private setting and again no costs are incurred by the NHS. It was acknowledged that the cost of laser is significantly above the prescription charge and is likely to be a very large financial cost for most people. For consistency, laser was considered in this analysis but results should be read in line with the detailed exploration within the discussion section of this report. When laser was assigned zero cost it was still assumed that a person would have a GP appointment but that a cost of contact with a consultant gynaecologist would not be incurred by the NHS.

Sensitivity analysis around continuation of effectiveness

During sensitivity analyses for time horizon and continuation of treatment effectiveness it was assumed that cost would remain the same as for the base-case analysis. This assumes that no treatment or directly related healthcare costs would be incurred after the first year of the model. This assumption was made as whilst there would almost certainly be these costs incurred after the first year it is likely that a large proportion of the cohort would have discontinued treatment or started second or a third line of treatments for their symptoms. As sequence of therapies were outside of the scope of the both the NMA and economic model we did not attempt to capture this in the model.

Table 19: List of model inputs and distributions used in the economic model

Input	Base-case estimate	Distribution in PSA	Source
Clinical outcomes			
Results from Bachman 2010 used for estimating transition probability coefficients (change on menopause rating scale)			
Ospemifene			
Dyspareunia (Baseline)	2.6	Fixed	Bachmann 2010
Dyspareunia (Change)	-1.19		
Vulvovaginal Dryness (Baseline)	2.4		
Vulvovaginal Dryness (Change)	-1.26		
Non-Hormonal moisturiser		Fixed	Bachmann 2010
Dyspareunia (Baseline)	2.7		
Dyspareunia (Change)	-0.889		
Vulvovaginal Dryness (Baseline)	2.4		

Input	Base-case estimate	Distribution in PSA	Source
Vulvovaginal Dryness (Change)	-0.837		
Estimated coefficients for transition probabilities		Fixed	Derived from Bachmann 2010
Effect of change in dyspareunia on transition to 'none' state	-0.215		
Effect of change in dryness on transition to 'none' state	-0.076		
Effect of change in dyspareunia on transition to 'mild' state	-0.0287		
Effect of change in dryness on transition to 'mild' state	0.0625		
Change in 0-3 scale Dyspareunia			
Non-hormonal moisturiser	0 (comparator)	Fixed	NMA
Prasterone	-0.29	Sampled from the simulated joint posterior distribution of the NMA	
Laser	-0.66	Sampled from the simulated joint posterior distribution of the NMA	
SERM	-0.16	Sampled from the simulated joint posterior distribution of the NMA	
Estriol	-0.36	Sampled from the simulated joint posterior distribution of the NMA	
Estradiol	-0.13	Sampled from the simulated joint posterior distribution of the NMA	
Change in 0-3 scale Vulvovaginal Dryness			
Non-hormonal moisturiser	0 (comparator)	Fixed	NMA
Prasterone	-0.26	Sampled from the simulated joint posterior distribution of the NMA	
Laser	-0.67	Sampled from the simulated joint posterior distribution of the NMA	
SERM	-0.28	Sampled from the simulated joint posterior distribution of the NMA	
Estriol	-0.21	Sampled from the simulated joint posterior distribution of the NMA	
Estradiol	-0.18	Sampled from the simulated joint posterior distribution of the NMA	

Input	Base-case estimate	Distribution in PSA	Source
Patient distribution Baseline			
Scored using menopause rating scale			
None	0	Fixed	Assumption
Mild	0		
Moderate + Severe	1		
Patient Distribution 12 weeks (Ospemifene)- Used to estimate transition matrices			
None	0.352	Fixed	Dymond 2021
Mild	0.263		
Moderate or severe	0.385		
Patient Distribution 12 weeks (Moisturiser/lubricant) – Used to estimate transition matrices			
None	0.255	Fixed	Dymond 2021
Mild	0.203		
Moderate or severe	0.542		
Costs			
12 Week course treatment			
Moisturiser/lubricant	£7.00	Triangular (Estimate ±50%)	BNF
Prasterone	£47.82	Triangular (Estimate ±50%)	BNF
Laser	£2502.50	Triangular (1500,3600)	Median various sources
Ospemifene	£125.50	Triangular (Estimate ±50%)	BNF
Estriol	£10.38	Triangular (Estimate ±50%)	BNF
Estradiol	£21.25	Triangular (Estimate ±50%)	BNF
GP Visit (in person)	£ 36.00		PSSRU 2022
GP Visit (telephone)	£ 14.27		
Gynaecology (First appointment)	£ 244.60		NHS Cost Collection 2020/21 cost code WF01B
Gynaecology (Subsequent appointments)	£ 196.09		NHS Cost Collection 2020/21 cost code WF01A
Appointments			

Input	Base-case estimate	Distribution in PSA	Source
Annual GP Visits			
None	1	Fixed	Assumption
Mild	1	Fixed	
Moderate/Severe	2	Equal probability (2-5)	
Utilities			
None	0.82	Beta (0.82, 0.010)	Di Bonaventura 2015
Mild	0.80	Beta (0.80, 0.015)	
Moderate	0.76	Beta (0.76, 0.018)	
Severe	0.68	Beta (0.68, 0.020)	
Combined Moderate/Severe	0.71	Combined from independent PSA estimates for moderate and severe	
Annual Discount rate			
Costs	3.5%	Fixed	NICE 2014
QALYS	3.5%		

Presentation of results

The results from the base-case analysis will be presented in terms of total costs and QALYs, incremental cost and QALYs, incremental cost effectiveness ratio (ICER) and incremental net monetary benefit (INMB). For all incremental outcomes these are compared to the reference treatment (non-hormonal moisturiser/lubricant) and are the outcome achieved for 1 person unless otherwise stated.

INMB is a representation of cost effectiveness where incremental QALY gain over the comparator intervention, are converted into a monetary value by multiplying by a willingness to pay for a QALY. For example, if an intervention had a QALY gain of 0.5 compared to the comparator and the willingness to pay for 1 QALY was £20,000, the monetary value of the QALY gain would be equal to £10,000. INMB is then calculated by subtracting total incremental cost from this monetary value of a QALY. Interventions which report a positive INMB are cost effective compared to the comparator with those reporting a negative value not being cost effective. The ‘preferred’ intervention would be the one which reports the highest INMB. Interventions can then be ordered by cost effectiveness relative to the comparator intervention. The ranking of interventions is not impacted by the choice of comparator intervention. For this analysis the ‘willingness to pay’ per QALY is equal to £20,000, the value below which NICE typically recommend interventions, unless otherwise stated.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were used in the base case

were replaced with values randomly drawn from distributions around the base-case values and results of the model recalculated. 1000 iterations of these results were sampled. Given that multiple interventions are considered by the model uncertainty was primarily presented on a cost effectiveness acceptability curve. (CEAC) A CEAC presents the probability of a particular intervention being the preferred option at different monetary values of willingness to pay for a QALY.

Effectiveness inputs were varied in the PSA using WinBUGS convergence diagnostics and output analysis (CODA) output, which gives all values from the joint posterior distribution of the NMA, from the primary NMAs for the dryness and dyspareunia outcomes which are included in the economic model. CODA outcomes were presented compared to non-hormonal moisturiser/lubricant as opposed to 'no active treatment' as in the NMA results. A total of 270,000 iterations from the CODA, presented on the same 0-3 scale used for the model inputs and sampled after the burn in iterations, were used in the model and full sets of odds ratios were sampled using a random number. The random number generator function in Excel was used to sample iterations and all had an identical probability of being sampled during any iteration of the PSA. Correlations between outcomes for different interventions are preserved by sampling for all from the same iteration of the NMA (Dias 2013).

Results

Base-case

Table 20 presents the base-case results from the economic model sorted by ascending total cost. Estriol has the lowest costs of all interventions considered and it was more effective than all other interventions except for laser. It is the preferred intervention when a £20,000 per QALY gained threshold is assumed and is dominant (both cost saving and health improving) compared to the reference treatment of non-hormonal moisturiser/lubricant. Laser was the most effective treatment option leading to more than 0.03 extra QALYs compared to moisturiser or lubricant. It was also the most expensive treatment and had an ICER of over £85,000 per QALY when compared directly to non-hormonal moisturiser/lubricant, significantly above values at which NICE recommend interventions. When INMB was considered and a £20,000 threshold per QALY gained considered, laser was ranked below all other treatments.

Table 20: Base-case results

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Moisturiser / lubricant	£99	0.7482				Reference	4
Estriol	£95	0.7653	-£3	0.0171	Dominant	£346	1
Estradiol	£110	0.7547	£12	0.0066	£1,786	£120	3
Prasterone	£134	0.7621	£35	0.0139	£2,548	£243	2
Ospemifene	£459	0.7562	£360	0.0080	£45,012	-£200	5
Laser	£2,826	0.7802	£2,727	0.0320	£85,124	-£2,087	6

[1]£20,000 per QALY threshold used

Deterministic sensitivity analysis

When in person GP visits are replaced with remote GP appointments there is no change in the ranking of the interventions when a £20,000 per QALY threshold is assumed. (Table 21)

Estriol remains the preferred intervention but is now cost increasing compared to the reference treatment of non-hormonal moisturiser/lubricant.

Table 21: Results with remote GP appointments assumed

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Moisturiser / lubricant	£43	0.7482				Reference	4
Estriol	£44	0.7653	£1	0.0171	£44	£342	1
Estradiol	£57	0.7547	£13	0.0066	£2,016	£118	3
Prasterone	£82	0.7621	£39	0.0139	£2,781	£240	2
Ospemifene	£405	0.7562	£362	0.0080	£45,239	-£202	5
Laser	£2,778	0.7802	£2,735	0.0320	£85,355	-£2,094	6

[1]£20,000 per QALY threshold used

Removing the cost of an appointment with a consultant gynaecologist prior to initiating treatment strongly improves the cost effectiveness of ospemifene with incremental costs compared to moisturiser/lubricant decreasing by over 60%. (Table 22) It is now also ranked above moisturiser/lubricant as the preferred option although is still below estriol, oestradiol and prasterone.

Table 22: Results with consultant gynaecologist visit prior to starting treatment removed

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Moisturiser / lubricant	£99	0.7482				Reference	5
Estriol	£95	0.7653	-£3	0.0171	Dominant	£346	1
Estradiol	£110	0.7547	£12	0.0066	£1,786	£120	3
Prasterone	£134	0.7621	£35	0.0139	£2,548	£243	2
Ospemifene	£214	0.7562	£115	0.0080	£14,436	£45	4
Laser	£2,581	0.7802	£2,483	0.0320	£85,489	-£2,094	6

[1]£20,000 per QALY threshold used

The base-case results were insensitive to the number of GP appointments for people who were in the moderate or severe group health state. For the ranking of treatments to change at all, 69 appointments would be needed by people in the moderate/severe health state. This change would only shift ospemifene from 5th ranked to the 4th ranked treatment. Over 400 GP visits would be needed for the top ranked treatment (estriol) to stop being the top ranked treatment. The same is also observed with the mild group with the number of visits needing to increase to 99 before estriol is no longer the preferred treatment, being overtaken by oestradiol.

Table 23 presents the results when effectiveness of interventions are assumed to taper over the first year of treatment back to the baseline value. Making this assumption did not change the ranking of preferred options compared to the base-case but did reduce the INMB of interventions with the higher total cost.

Table 23: Results effectiveness of interventions taper over one year

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Moisturiser / lubricant	£99	0.7295				Reference	4
Estriol	£95	0.7392	-£3	0.0097	Dominant	£197	1
Estradiol	£110	0.7332	£12	0.0037	£3,160	£63	3
Prasterone	£134	0.7374	£35	0.0079	£4,508	£122	2
Ospemifene	£459	0.7340	£360	0.0045	£79,636	-£270	5
Laser	£2,826	0.7476	£2,727	0.0181	£150,603	-£2,365	6

[1]£20,000 per QALY threshold used

Table 24 shows the results of the economic model when a 10 year time horizon is assumed with continuing treatment effect. This analysis favours more expensive treatments with laser, whilst being the most expensive of the treatments considered also becomes the preferred option at a threshold of £20,000 per QALY. Moisturiser whilst the second least costly intervention is the least preferred of the 6 interventions considered by the model. Other interventions have kept their ranking compared to the base case results.

Table 24: Results assuming a ten-year time horizon and continued effect

	Total cost	Total QALY	Inc.Cost	Inc.QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Moisturiser / lubricant	£99	6.4826				Reference	6
Estriol	£95	6.6468	-£3	0.1643	Dominant	£3,289	2
Estradiol	£110	6.5457	£12	0.0631	£186	£1,251	4
Prasterone	£134	6.6162	£35	0.1336	£265	£2,637	3
Ospemifene	£459	6.5594	£360	0.0768	£4,689	£1,176	5
Laser	£2,826	6.7901	£2,727	0.3076	£8,867	£3,424	1

[1]£20,000 per QALY threshold used

When a tapering effect over 10 years is assumed then the three preferred treatments, estriol, prasterone and oestradiol remain the same (and in the same order) as for the base-case results. Non-hormonal moisturised/lubricant is the least preferred option ranking below all other treatments. Laser and ospemifene increase their ranking compared to the base-case but are still less preferred than other interventions.

Table 25: Results assuming a ten-year time horizon and tapering effect

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Moisturiser / lubricant	£99	6.2908				Reference	6
Estriol	£95	6.3786	-£3	0.0878	Dominant	£1,759	1
Estradiol	£110	6.3245	£12	0.0337	£348	£663	3
Prasterone	£134	6.3622	£35	0.0714	£497	£1,392	2

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Ospemifene	£459	6.3318	£360	0.0410	£8,776	£460	5
Laser	£2,826	6.4551	£2,727	0.1643	£16,597	£559	4

[1]£20,000 per QALY threshold used

Table 26 shows the results when the treatment cost of 'over-the-counter' interventions are excluded. Under this scenario laser is both the least costly to the NHS and also leads to the highest gains in QALYs. Oestradiol drops one place in the ranking but is now cost saving to the NHS and health improving compared to non-hormonal moisturiser/lubricants.

Table 26: Cost of over-the-counter interventions excluded

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Moisturiser / lubricant	£92	0.7482					5
Laser	£79	0.7802	-£12	0.0320	Dominant	£653	1
Estradiol	£89	0.7547	-£3	0.0066	Dominant	£134	4
Estriol	£95	0.7653	£4	0.0171	£219	£339	2
Prasterone	£134	0.7621	£42	0.0139	£3,051	£236	3
Ospemifene	£459	0.7562	£367	0.0080	£45,887	-£207	6

[1]£20,000 per QALY threshold used

When local vaginal oestrogen is excluded from the analysis prasterone was returned as the most cost effective intervention. Prasterone has a ICER of around £2,500 per QALY below the £20,000 per QALY threshold. Ospemifene and laser were both significantly above this value. (Table 27)

Table 27: Base case results of interventions for which eostrogen treatments are not indicated

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER (vs Reference)	INMB[1]	Rank[1]
Moisturiser/ lubricant	£99	0.7482				Reference	2
Prasterone	£134	0.7621	£35	0.0139	£2,548	£243	1
Ospemifene	£459	0.7562	£360	0.0080	£45,012	-£200	3
Laser	£2,826	0.7802	£2,727	0.0320	£85,124	-£2,087	4

[1]£20,000 per QALY threshold used

Threshold analysis

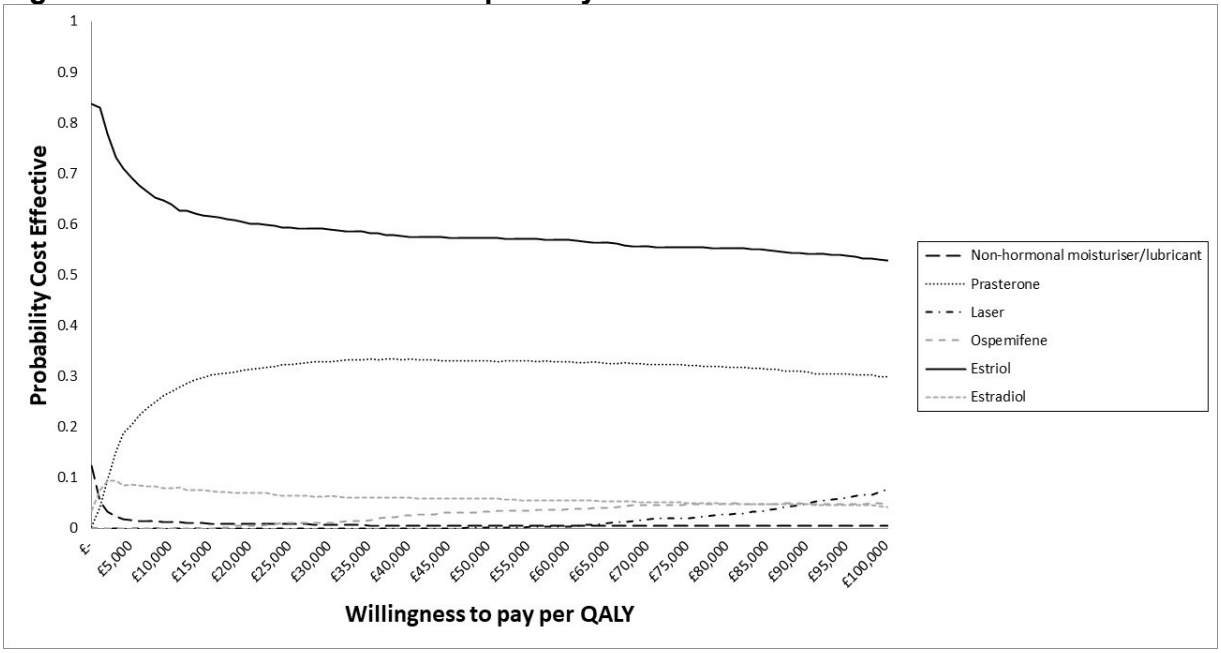
For laser to become the preferred option at a cost per QALY gained threshold of £20,000 the cost of the intervention the estimated cost of £2,502 would need to be reduced to £70 to be the cost effective option or £315 if the intervention could be prescribed by a GP.

Probabilistic sensitivity analysis

Figure 16 shows the cost effectiveness acceptability curve from the PSA. At a threshold of £20,000 per additional QALY, the value at which NICE usually recommend interventions, estriol has a 60.0% probability of being the preferred intervention with prasterone (31.4%)

and oestradiol (7.0%) being the second and third most probable treatments. As the willingness-to-pay per additional QALY increase the probability of laser being the preferred option increase. However even at thresholds of £100,000 per QALY the probability of it being the preferred option was 7.7%. Laser only became the preferred option at thresholds above £270,000 per QALY.

Figure 16: Cost effectiveness acceptability curve



Discussion

The results of the economic model suggest that estriol is the preferred option for treatment of genitourinary symptoms associated with the menopause. This conclusion was robust to various sensitivity analyses and there was a greater than 60% probability of it being the preferred treatment in the PSA.

Laser (and other interventions) were estimated to be more effective in terms of total QALYs than estriol, however this was not achieved at a cost per QALY at which NICE typically recommend interventions. Such interventions were only the preferred option when long continuing estimates of effectiveness were considered or there were significant reductions in the cost of the intervention. Laser was estimated to have a larger increase in QALYs based on favourable estimates from the accompanying NMA. The committee were cautious of the results around laser given the relatively small patient group informing the outcome (only two studies of 88 patients in total) compared to other interventions in the NMA. Despite not being explored formally given the small number of trials there was also some concern over publication bias for the laser intervention given the relatively smaller size of the included RCTs. Even if the results of the NMA are accepted as an accurate estimate of the effectiveness of laser it still needed favourable assumptions around costs and long-term effectiveness. No NHS prices were identified for laser in the usual sources and thus cost was estimated from sources in the private sector. It is probable that if laser was widely available in the NHS it could benefit from economies of scale and removal of any profit margins making the unit cost of the intervention significantly cheaper. However, in the base-case analysis a reduction in price of more than 96% was needed for it to become the

preferred option an amount the committee did not see as feasible. It was acknowledged that it was still unclear how laser would work in the NHS if it was to become an available treatment. The committee assumed, like ospemifene, that it was a specialist treatment and would first require an appointment with a consultant gynaecologist. Even if this assumption was removed and treatment could be prescribed directly from a GP, the cost of laser would need to be reduced by 85% to become the preferred option. Again, the committee thought this large a reduction was unlikely. Given the uncertainty around the NMA results and the cost of laser in an NHS setting this gave support for a research recommendation around laser which included outcomes associated with cost effectiveness such as resource use and quality of life. When local vaginal oestrogen therapies were not indicated or appropriate for an individual prasterone was the preferred choice.

It was also considered that using the NHS cost collection from 2020/21, despite being the most recent version available, may overestimate costs as the data would have been collected during the covid-19 pandemic when the cost of appointments would have been higher. A first and follow-up appointment in gynaecology (currency code WF10B and WF10A) was £172.03 and £144.98 in the 2019/20 cost collection, a cost reduction of between 25-30% for both. Using NHS Cost Collection from previous years may give more applicable costs but given that reducing these costs to zero (as above) did not change the conclusions of the model the choice of cost year would also have no impact on conclusions.

When it was assumed that any costs of treatments available ‘over-the-counter’ were removed then laser was the preferred option. Currently, laser treatment for genitourinary symptoms associated with the menopause are almost exclusively carried out in the private sector. The cost of laser treatment is also significantly more costly than ‘over-the-counter’ treatments often covered in NICE guidance and would represent a large cost to most individuals. The committee acknowledged that costs such as time off work and over-the-counter pain medication were outside of the scope of the model and may represent a significant cost to most people. These could potentially be reduced with more effective treatment. Given the uncertainty around the results and the large potential cost, even when other avoided costs to individuals are considered no recommendations were made to signpost to this outside of NHS treatment. Oestradiol was the preferred option in this analysis if laser was not included.

The outcomes of 3 of the intended NMAs were not included directly into the model. Laser, prasterone and oestradiol performed well for discomfort. Inclusion of these outcomes may have increased the estimated quality of life for these interventions and increased their probability of being the preferred option. Adverse events and discontinuation of treatment were excluded from the analysis but as discussed earlier inclusion of these outcomes would be unlikely to alter conclusions.

One previous economic evaluation was identified for this topic (Dymond 2021). Although this was in a patient group for which oestrogen-based treatment was contraindicated or otherwise unsuitable and had a more limited number of interventions. This study was highly applicable and with potentially serious methodological limitations although closely followed the NICE guideline methodology. Despite this our conclusions somewhat differed to the Dymond 2021 study which found Ospemifene to be a cost effective intervention with an estimated ICER for ospemifene compared to moisturiser or lubricant of £14,138 per QALY.

This was robust to deterministic and probabilistic sensitivity analysis. There were a number of reasons for this difference in conclusions. Firstly, Dymond 2021 used data from the Portman 2014 RCT which was included in the accompanying NMA. Results from that study estimated an effectiveness of ospemifene compared to moisturiser/lubricant higher than the accompanying NMA for the two key inputs to this model of dyspareunia and vuvlvovaginal dryness. If the NMA results were inputted into Dymond 2021 it would lead to a higher estimate of the ICER. Given that the NMA synthesised a number of RCTs, including Portman 2014, and consequently had more precise estimates from a larger pool of trial participants, the committee lent greater weight to the outcomes of this analysis as opposed to one individual study. Dymond 2021 also used a lifetime time horizon with an assumption of no treatment waning effect (reduction in effectiveness) following the first year of treatment. A sensitivity analysis was also carried out that did not significantly alter conclusion returning a similar ICER to the Dymond 2021 base-case of £14,167 per QALY. This analysis is most similar to our 10 year time horizon with continuation of effectiveness where ospemifene was a cost effective option when compared directly to moisturiser or lubricant. Thirdly, this model did not include adverse events but as discussed previously this only accounted for a small proportion of costs and QALYs in the two models. Despite the difference in results of the model the conclusions from the committee were identical to the discussion of Dymond 2021 and the Scottish Medicines Consortium in that ospemifene could be an efficient use of NHS resources where oestrogen treatments were not indicated or where they had previously been ineffective, or treatment effectiveness had waned.

Overall, estriol and oestradiol appeared to be the cost effective option for genitourinary symptoms associated with the menopause. Where these were not suitable for an individual prasterone was the preferred choice. More expensive interventions such as laser or ospemifene were cost effective when assumptions that effectiveness would remain over a longer term were assumed. Lasers returned good effectiveness and higher QALYs than other interventions but at a high cost. Given uncertainty around the shorter andlonger term health outcomes and costs of lasers if they were provided on the NHS there is likely to be a benefit from further research in this area.

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Dymond A, Holmes H, McMaster J, Craig J, Davies H, Mealing S, Perard R. Economic Evaluation of Senshio®(Ospemifene) for the Treatment of Vulvovaginal Atrophy in Scotland. Applied Health Economics and Health Policy. 2021 Jan;19:123-32.

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10

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Excluded effectiveness studies

Table 28: Studies meeting review protocol criteria that were excluded from the NMA

Study	Code [Reason]
Bygdeman, M and Swahn, M L (1996) Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 23 (3ccgynaecologyandfertility): 259-263	- Study met review protocol criteria but not included in NMA - zero events in both arms
Cruff, Jason and Khandwala, Salil (2021) A Double-Blind Randomized Sham-Controlled Trial to Evaluate the Efficacy of Fractional Carbon Dioxide Laser Therapy on Genitourinary Syndrome of Menopause. The journal of sexual medicine 18 (4): 761-769	- Study met review protocol criteria but not included in NMA - zero events in both arms
Dessole, S, Rubattu, G, Ambrosini, G et al. (2004) Efficacy of low-dose intravaginal estriol on urogenital aging in postmenopausal women. Menopause (New York, N.Y.) 11 (1ccincontinenceccgynaecologyandfertility): 49-56	- Study met review protocol criteria but not included in NMA - outcomes measured at ≥14 weeks follow-up
Eftekhar, Tahereh, Forooghifar, Tahereh, Khalili, Tahereh et al. (2020) The Effect of the CO2 Fractional Laser or Premarin Vaginal Cream on Improving Sexual Function in Menopausal Women: A Randomized Controlled Trial. Journal of lasers in medical sciences 11 (3): 292-298	- Study met review protocol criteria but not included in NMA - laser trial which did not include sham laser as a placebo comparator
Goldstein, S R, Bachmann, G A, Koninckx, P R et al. (2014) Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric 17 (2): 173-182	- Study met review protocol criteria but not included in NMA - outcomes measured at ≥14 weeks follow-up
Hosseinzadeh, P, Ghahiri, A, Daneshmand, F et al. (2015) A comparative study of vaginal estrogen cream and sustained-release estradiol vaginal tablet (Vagifem) in the treatment of atrophic vaginitis in Isfahan, Iran in 2010-2012. Journal of research in medical sciences 20 (12ccgynaecologyandfertility): 1160-1165	- Study met review protocol criteria but not included in NMA - outcome (discontinuation due to adverse events) not reported in both arms
Jokar, Azam, Davari, Tayebe, Asadi, Nasrin et al. (2016) Comparison of the hyaluronic acid vaginal cream and conjugated estrogen used in treatment of vaginal atrophy of menopause women: A randomized controlled clinical trial. Int. J. Community Based Nurs. Midwifery 4 (1): 69-78	- Study met review protocol criteria but not included in NMA - zero events in both arms
Lillemon, Jennifer Nicole, Karstens, Lisa, Nardos, Rahel et al. (2022) The Impact of Local Estrogen on the Urogenital Microbiome in Genitourinary Syndrome of Menopause: A Randomized-Controlled Trial. Female pelvic medicine & reconstructive surgery 28 (6): e157-e162	- Study met review protocol criteria but not included in NMA - zero events in both arms
Paraiso, Marie Fidela R, Ferrando, Cecile A, Sokol, Eric R et al. (2020) A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial. Menopause (New York, N.Y.) 27 (1): 50-56	- Study met review protocol criteria but not included in NMA - laser trial which did not include sham laser as a placebo comparator

Study	Code [Reason]
Politano, Carlos A, Costa-Paiva, Lucia, Aguiar, Luiza B et al. (2019) Fractional CO2 laser versus promestriene and lubricant in genitourinary syndrome of menopause: a randomized clinical trial. Menopause (New York, N.Y.) 26 (8): 833-840	- Study met review protocol criteria but not included in NMA - laser trial which did not include sham laser as a placebo comparator
Quick, Allison M, Dockter, Travis, Le-Rademacher, Jennifer et al. (2021) Pilot study of fractional CO2 laser therapy for genitourinary syndrome of menopause in gynecologic cancer survivors. Maturitas 144: 37-44	- Study met review protocol criteria but not included in NMA - zero events in both arms
Rioux, J E, Devlin, C, Gelfand, M M et al. (2000) 17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause 7 (3): 156-161	- Study met review protocol criteria but not included in NMA - outcomes measured at ≥14 weeks follow-up
Simon, J, Nachtigall, L, Gut, R et al. (2008) Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. Obstetrics and gynecology 112 (5ccgynaecologyandfertility): 1053-1060	- Study met review protocol criteria but not included in NMA - outcomes measured at ≥14 weeks follow-up
Simunić, V, Banović, I, Ciglar, S et al. (2003) Local estrogen treatment in patients with urogenital symptoms. International journal of gynaecology and obstetrics 82 (2ccgynaecologyandfertility): 187-197	- Study met review protocol criteria but not included in NMA - outcome (discontinuation due to adverse events) not reported in both arms
Voipio, S K, Komi, J, Kangas, L et al. (2002) Effects of ospemifene (FC-1271a) on uterine endometrium, vaginal maturation index, and hormonal status in healthy postmenopausal women. Maturitas 43 (3): 207-214	- Study met review protocol criteria but not included in NMA - zero events in both arms
Wamsley, Christine, Kislevitz, Mikaela, Vingan, Nicole R et al. (2022) A Randomized, Placebo-Controlled Trial Evaluating the Single and Combined Efficacy of Radiofrequency and Hybrid Fractional Laser for Nonsurgical Aesthetic Genital Procedures in Post-Menopausal Women. Aesthetic surgery journal	- Study met review protocol criteria but not included in NMA - outcome (discontinuation due to adverse events) not reported in both arms

1 **Table 29: Excluded studies and reasons for their exclusion**

Study	Code [Reason]
Aguiar, Luiza Borges, Politano, Carlos Alberto, Costa-Paiva, Lucia et al. (2020) Efficacy of Fractional CO2 Laser, Promestriene, and Vaginal Lubricant in the Treatment of Urinary Symptoms in Postmenopausal Women: A Randomized Clinical Trial. Lasers in surgery and medicine 52 (8): 713-720	- Outcome - reported outcomes do not match the review protocol
Archer, David F, Labrie, Fernand, Montesino, Marlene et al. (2017) Comparison of intravaginal 6.5mg (0.50%) prasterone, 0.3mg conjugated estrogens and 10mug estradiol on symptoms of vulvovaginal atrophy. The Journal of steroid biochemistry and molecular biology 174: 1-8	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Barton, Debra L, Shuster, Lynne T, Dockter, Travis et al. (2018) Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 26 (4): 1335-1343	- Outcome - reported outcomes do not match the review protocol
Benoit, T, Leguevaque, P, Roumiguié, M et al. (2015) [Use of local estrogenotherapy in urology and pelviperineology: A systematic review]. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie 25 (11): 628-35	- Language - article not in English
Biehl, Colton; Plotsker, Olivia; Mirkin, Sebastian (2019) A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. Menopause (New York, N.Y.) 26 (4):	- Systematic review. Included studies checked for eligibility

Study	Code [Reason]
431-453	and added if relevant for inclusion
Bosak, Zahra, Iravani, Mina, Moghimipour, Eskandar et al. (2022) Effect of Chamomile Vaginal Gel on the Sexual Function in Postmenopausal Women: A Double-Blind Randomized Controlled Trial. The journal of sexual medicine 19 (6): 983-994	- Duplicate
Bosak, Zahra, Iravani, Mina, Moghimipour, Eskandar et al. (2020) Evaluation of the influence of chamomile vaginal gel on dyspareunia and sexual satisfaction in postmenopausal women: A randomized, double-blind, controlled clinical trial. Avicenna journal of phytomedicine 10 (5): 481-491	- Duplicate
Bruyniks, N, Biglia, N, Palacios, S et al. (2017) Systematic indirect comparison of ospemifene versus local estrogens for vulvar and vaginal atrophy. Climacteric : the journal of the International Menopause Society 20 (3): 195-204	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Bruyniks, N, Nappi, R E, Castelo-Branco, C et al. (2016) Effect of ospemifene on moderate or severe symptoms of vulvar and vaginal atrophy. Climacteric : the journal of the International Menopause Society 19 (1): 60-5	- Study design - not a systematic review, randomised controlled trial
Buckler, Helen; Al-Azzawi, Farook; Group, U K V R Multicentre Trial (2003) The effect of a novel vaginal ring delivering oestradiol acetate on climacteric symptoms in postmenopausal women. BJOG 110 (8): 753-759	- Outcome - reported outcomes do not match the review protocol
Buzzaccarini, G, Marin, L, Noventa, M et al. (2021) Hyaluronic acid in vulvar and vaginal administration: evidence from a literature systematic review. Climacteric : the journal of the International Menopause Society 24 (6): 560-571	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Capobianco, Giampiero, Donolo, Ermes, Borghero, Gianna et al. (2012) Effects of intravaginal estriol and pelvic floor rehabilitation on urogenital aging in postmenopausal women. Arch. Gynecol. Obstet. 285 (2): 397-403	- Intervention - interventions in the study do not match the review protocol
Casper, F and Petri, E (1999) Local treatment of urogenital atrophy with an estradiol-releasing vaginal ring: a comparative and a placebo-controlled multicenter study. Vaginal Ring Study Group. International urogynecology journal and pelvic floor dysfunction 10 (3ccgynaecologyandfertility): 171-176	- Outcome - reported outcomes do not match the review protocol
Coelingh Bennink, Herjan J T, Verhoeven, Carole, Zimmerman, Yvette et al. (2016) Clinical effects of the fetal estrogen estetrol in a multiple-rising-dose study in postmenopausal women. Maturitas 91: 93-100	- Outcomes do not match the review protocol
Constantine, G.D., Archer, D.F., Pollycove, R. et al. (2016) Ospemifene's effect on vasomotor symptoms: A post hoc Analysis of phase 2 and 3 clinical data. Menopause 23 (9): 957-964	- Study design - not a systematic review, randomised controlled trial, or observational study
Constantine, G, Graham, S, Portman, D J et al. (2015) Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric 18 (2): 226-232	- Outcome - reported outcomes do not match the review protocol
Constantine, Ginger D; Goldstein, Steven R; Archer, David F (2015) Endometrial safety of ospemifene: results of the phase 2/3 clinical development program. Menopause (New York, N.Y.) 22 (1): 36-43	- Outcome - reported outcomes do not match the review protocol
Constantine, Ginger D, Graham, Shelli, Lapane, Kate et al. (2019) Endometrial safety of low-dose vaginal estrogens in menopausal women: a	- Intervention - interventions in the

Study	Code [Reason]
systematic evidence review. Menopause (New York, N.Y.) 26 (7): 800-807	study do not match the review protocol
Constantine, Ginger D, Simon, James A, Pickar, James H et al. (2018) Estradiol vaginal inserts (4 microg and 10 microg) for treating moderate to severe vulvar and vaginal atrophy: a review of phase 3 safety, efficacy and pharmacokinetic data. Current medical research and opinion 34 (12): 2131-2136	- Outcome - reported outcomes do not match the review protocol
Constantine, Ginger D, Simon, James A, Pickar, James H et al. (2017) The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. Menopause 24 (4): 409-416	- Trial already included, this publication does not include additional relevant outcome data
Constantine, Ginger, Millheiser, Leah S, Kaunitz, Andrew M et al. (2019) Early onset of action with a 17beta-estradiol, softgel, vaginal insert for treating vulvar and vaginal atrophy and moderate to severe dyspareunia. Menopause (New York, N.Y.) 26 (11): 1259-1264	- Trial already included, this publication does not include additional relevant outcome data
Crandall, Carolyn J; Diamant, Allison; Santoro, Nanette (2020) Safety of vaginal estrogens: a systematic review. Menopause (New York, N.Y.) 27 (3): 339-360	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Daneshmand, F, Hosseinzadeh, P, Ghahiri, A et al. (2014) A comparative study of vaginal estrogen cream and sustained-released estradiol vaginal tablet (vagifem) in the treatment of atrophic vaginitis among postmenopausal women. Iranian journal of reproductive medicine 12 (6suppl1ccgynaecologyandfertility): 12-13	- Duplicate
Dayal, Molina, Sammel, Mary D, Zhao, Jing et al. (2005) Supplementation with DHEA: effect on muscle size, strength, quality of life, and lipids. Journal of women's health (2002) 14 (5): 391-400	- Outcome - reported outcomes do not match the review protocol
De Seta, F, Caruso, S, Di Lorenzo, G et al. (2021) Efficacy and safety of a new vaginal gel for the treatment of symptoms associated with vulvovaginal atrophy in postmenopausal women: A double-blind randomized placebo-controlled study. Maturitas 147: 34-40	- Intervention - interventions in the study do not match the review protocol
Delgado, J L, Estevez, J, Radicioni, M et al. (2016) Pharmacokinetics and preliminary efficacy of two vaginal gel formulations of ultra-low-dose estriol in postmenopausal women. Climacteric 19 (2): 172-180	- Outcome - reported outcomes do not match the review protocol
Derzko, Christine M; Rohrich, Sebastian; Panay, Nick (2020) Does age at the start of treatment for vaginal atrophy predict response to vaginal estrogen therapy? Post hoc analysis of data from a randomized clinical trial involving 205 women treated with 10 mug estradiol vaginal tablets. Menopause (New York, N.Y.) 28 (2): 113-118	- Study design - not a systematic review, randomised controlled trial, or observational study
Di Donato, Violante, Schiavi, Michele Carlo, Iacobelli, Valentina et al. (2019) Ospemifene for the treatment of vulvar and vaginal atrophy: A meta-analysis of randomized trials. Part II: Evaluation of tolerability and safety. Maturitas 121: 93-100	- Outcome - reported outcomes do not match the review protocol
Di Donato, Violante, Schiavi, Michele Carlo, Iacobelli, Valentina et al. (2019) Ospemifene for the treatment of vulvar and vaginal atrophy: A meta-analysis of randomized trials. Part I: Evaluation of efficacy. Maturitas 121: 86-92	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Diem, Susan J, Guthrie, Katherine A, Mitchell, Caroline M et al. (2018)	- Outcome - reported

Study	Code [Reason]
Effects of vaginal estradiol tablets and moisturizer on menopause-specific quality of life and mood in healthy postmenopausal women with vaginal symptoms: a randomized clinical trial. Menopause (New York, N.Y.) 25 (10): 1086-1093	outcomes do not match the review protocol
Dos Santos, Carlos Campagnaro M, Uggioni, Maria Laura R, Colonetti, Tamy et al. (2021) Hyaluronic Acid in Postmenopause Vaginal Atrophy: A Systematic Review. The journal of sexual medicine 18 (1): 156-166	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Dutra, Paula Fernanda Santos Pallone, Heinke, Thais, Pinho, Stella Catunda et al. (2021) Comparison of topical fractional CO2 laser and vaginal estrogen for the treatment of genitourinary syndrome in postmenopausal women: a randomized controlled trial. Menopause (New York, N.Y.) 28 (7): 756-763	- Outcome - reported outcomes do not match the review protocol
Eftekhar, Tahereh, Forooghifar, Tahereh, Khalili, Tahereh et al. (2020) The Effect of the CO2 Fractional Laser or Premarin Vaginal Cream on Improving Sexual Function in Menopausal Women: A Randomized Controlled Trial. Journal of lasers in medical sciences 11 (3): 292-298	- Comparison - did not include sham laser as a placebo comparator, meaning that effects were likely to be inflated due to failing to blind participants to the allocated intervention
Ekin, Murat, Yaşar, Levent, Savan, Kadir et al. (2011) The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. Arch. Gynecol. Obstet. 283 (3): 539-543	- Outcome - reported outcomes do not match the review protocol
Espitia-de la Hoz, FJ and Orozco-Gallego, H (2018) Estriol vs. Conjugated estrogens of equine origin in the treatment of the genitourinary syndrome of menopause. Ginecologia y obstetricia de Mexico 86 (2): 117-126	- Language - article not in English Not in English
Fernandes, Tatiane, Costa-Paiva, Lucia Helena, Pedro, Adriana Orcesi et al. (2016) Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. Menopause 23 (7): 792-798	- Outcome - reported outcomes do not match the review protocol
Fernandes, Tatiane, Pedro, Adriana O, Baccaro, Luiz F et al. (2018) Hormonal, metabolic, and endometrial safety of testosterone vaginal cream versus estrogens for the treatment of vulvovaginal atrophy in postmenopausal women: a randomized, placebo-controlled study. Menopause (New York, N.Y.) 25 (6): 641-647	- Outcome - reported outcomes do not match the review protocol
Filippini, Maurizio, Porcari, Irene, Ruffolo, Alessandro F et al. (2022) CO2-Laser therapy and Genitourinary Syndrome of Menopause: A Systematic Review and Meta-Analysis. The journal of sexual medicine 19 (3): 452-470	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Flint, R, Cardozo, L, Grigoriadis, T et al. (2019) Rationale and design for fractional microablative CO2 laser versus photothermal non-ablative erbium:YAG laser for the management of genitourinary syndrome of menopause: a non-inferiority, single-blind randomized controlled trial. Climacteric : the journal of the International Menopause Society 22 (3): 307-311	- Article is a review protocol
FlorencioSilva, Rinaldo, Simões, Ricardo Santos, Girão, João Henrique Rodrigues Castello et al. (2017) Treatment of vaginal atrophy of women in postmenopausal. Reprod. clim 32 (1): 43-47	- Language - article not in English
Foidart, J M; Vervliet, J; Buytaert, P (1991) Efficacy of sustained-release vaginal oestriol in alleviating urogenital and systemic climacteric complaints. Maturitas 13 (2ccgynaecologyandfertility): 99-107	- Outcome - reported outcomes do not match the review

Study	Code [Reason]
	protocol
Freedman, Murray, Kaunitz, Andrew M, Reape, Kathleen Z et al. (2009) Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy. Menopause 16 (4): 735-741	- Outcome - reported outcomes do not match the review protocol
Gibson, Carolyn J, Huang, Alison J, Larson, Joseph C et al. (2020) Patient-centered change in the day-to-day impact of postmenopausal vaginal symptoms: results from a multicenter randomized trial. American journal of obstetrics and gynecology 223 (1): 99e1-99e9	- Outcome - reported outcomes do not match the review protocol
Goldstein, I, Simon, J, Kaunitz, A et al. (2019) Evaluation of Vulvar Health from Photographs in a Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Efficacy and Safety of Ospemifene in 631 Postmenopausal Women (age 40-80)with Moderate to Severe Vaginal Dryness. Journal of sexual medicine. Conference: ISSWSH/ISSM joint meeting, 'it takes 2 to tango'. United states 16suppl3 (6): S8-S9	- Conference abstract
Goldstein, Irwin, Simon, James A, Kaunitz, Andrew M et al. (2019) Effects of ospemifene on genitourinary health assessed by prospective vulvar-vestibular photography and vaginal/vulvar health indices. Menopause (New York, N.Y.) 26 (9): 994-1001	- Outcome - reported outcomes do not match the review protocol
Goldstein, S, Kellogg Spadt, S, Murina, F et al. (2020) Safety and Efficacy of CO2 Fractional Laser Therapy in Women with Vestibulodynia. Journal of sexual medicine. Conference: 20th annual fall scientific meeting of SMSNA. Omni nashville hotel, united states 17suppl1: 9	- Conference abstract
Golmakani, Nahid, Parnan Emamverdikhan, Aazam, Zarifian, Ahmadreza et al. (2019) Vitamin E as alternative local treatment in genitourinary syndrome of menopause: a randomized controlled trial. Int. Urogynecol. J. 30 (5): 831-837	- Outcome - reported outcomes do not match the review protocol
Guo, Julia Z, Souders, Colby, McClelland, Lynn et al. (2020) Vaginal laser treatment of genitourinary syndrome of menopause: does the evidence support the FDA safety communication?. Menopause (New York, N.Y.) 27 (10): 1177-1184	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Ke, Yuyong, Labrie, Fernand, Gonthier, Renaud et al. (2015) Serum levels of sex steroids and metabolites following 12 weeks of intravaginal 0.50% DHEA administration. The Journal of steroid biochemistry and molecular biology 154: 186-96	- Outcome - reported outcomes do not match the review protocol
Khamis, Yasser, Abdelhakim, Ahmed Mohamed, Labib, Kareem et al. (2021) Vaginal CO2 laser therapy versus sham for genitourinary syndrome of menopause management: a systematic review and meta-analysis of randomized controlled trials. Menopause (New York, N.Y.) 28 (11): 1316-1322	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Kingsberg, Sheryl A, Kroll, Robin, Goldstein, Irwin et al. (2017) Patient acceptability and satisfaction with a low-dose solubilized vaginal estradiol softgel capsule, TX-004HR. Menopause (New York, N.Y.) 24 (8): 894-899	- Outcome - reported outcomes do not match the review protocol
Klap, J, Campagne-Loiseau, S, Berrogain, N et al. (2021) [Vaginal LASER therapy for genito-urinary disorders: A systematic review and statement from the Committee for Female Urology and Pelviperineology of the French Association of Urology]. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie	- Language - article not in English
Kovachev, Stefan Miladinov and Kovachev, Miladin Stefanov (2022) Genitourinary syndrome, local oestrogen therapy and endometrial pathology: a single-centre, randomised study. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology: 1-4	- Outcome - reported outcomes do not match the review protocol

Study	Code [Reason]
Kroll, Robin, Archer, David F, Lin, Yuhua et al. (2018) A randomized, multicenter, double-blind study to evaluate the safety and efficacy of estradiol vaginal cream 0.003% in postmenopausal women with dyspareunia as the most bothersome symptom. Menopause 25 (2): 133-138	- Trial already included, this publication does not include additional relevant outcome data
Labrie, F, Archer, D F, Bouchard, C et al. (2011) Intravaginal dehydroepiandrosterone (prasterone), a highly efficient treatment of dyspareunia. Climacteric 14 (2): 282-288	- Trial already included, this publication does not include additional relevant outcome data
Labrie, Fernand (2010) Intravaginal DHEA, by a strictly local action, exerts beneficial effects on both vaginal atrophy symptoms and sexual dysfunction. Hormone molecular biology and clinical investigation 4 (1): 499-507	- Study design - not a systematic review, randomised controlled trial, or observational study
Labrie, Fernand, Archer, David F, Martel, Celine et al. (2017) Combined data of intravaginal prasterone against vulvovaginal atrophy of menopause. Menopause (New York, N.Y.) 24 (11): 1246-1256	- Trial already included, this publication does not include additional relevant outcome data
Labrie, Fernand, Archer, David, Bouchard, Celine et al. (2009) Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause (New York, N.Y.) 16 (5): 923-31	- Outcome - reported outcomes do not match the review protocol
Labrie, Fernand, Archer, David, Bouchard, Celine et al. (2014) Lack of influence of dyspareunia on the beneficial effect of intravaginal prasterone (dehydroepiandrosterone, DHEA) on sexual dysfunction in postmenopausal women. The journal of sexual medicine 11 (7): 1766-85	- Trial already included, this publication does not include additional relevant outcome data
Labrie, Fernand, Archer, David, Bouchard, Céline et al. (2010) High internal consistency and efficacy of intravaginal DHEA for vaginal atrophy. Gynecol. Endocrinol. 26 (7): 524-532	- Trial already included, this publication does not include additional relevant outcome data
Labrie, Fernand, Cusan, Leonello, Gomez, Jose Luis et al. (2008) Effect of intravaginal DHEA on serum DHEA and eleven of its metabolites in postmenopausal women. The Journal of steroid biochemistry and molecular biology 111 (35): 178-94	- Outcome - reported outcomes do not match the review protocol
Labrie, Fernand, Derogatis, Leonard, Archer, David F et al. (2015) Effect of intravaginal prasterone on sexual dysfunction in postmenopausal women with vulvovaginal atrophy. J. Sex. Med. 12 (12): 2401-2412	- Trial already included, this publication does not include additional relevant outcome data
Larmo, Petra S, Yang, Baoru, Hyssälä, Juha et al. (2014) Effects of sea buckthorn oil intake on vaginal atrophy in postmenopausal women: a randomized, double-blind, placebo-controlled study. Maturitas 79 (3): 316-321	- Intervention - interventions in the study do not match the review protocol
Lee, Arum, Kim, Tae Hee, Lee, Hae Hyeog et al. (2018) Therapeutic Approaches to Atrophic Vaginitis in Postmenopausal Women: A Systematic Review with a Network Meta-analysis of Randomized Controlled Trials. Journal of menopausal medicine 24 (1): 1-10	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Lethaby, Anne; Ayeleke, Reuben Olugbenga; Roberts, Helen (2016) Local oestrogen for vaginal atrophy in postmenopausal women. The Cochrane database of systematic reviews: cd001500	- Systematic review. Included studies checked for eligibility

Study	Code [Reason]
	and added if relevant for inclusion
Li, Bohan, Duan, Hua, Chang, Yanan et al. (2021) Efficacy and safety of current therapies for genitourinary syndrome of menopause: A Bayesian network analysis of 29 randomized trials and 8311 patients. Pharmacological research 164: 105360	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Li, Fiona, Picard-Fortin, Vanessa, Maheux-Lacroix, Sarah et al. (2021) The Efficacy of Vaginal Laser and Other Energy-based Treatments on Genital Symptoms in Postmenopausal Women: A Systematic Review and Meta-analysis. Journal of minimally invasive gynecology 28 (3): 668-683	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Lillemon, J, Karstens, L, Nardos, R et al. (2020) The impact of a vaginal estrogen ring vs placebo on the vaginal microbiome in postmenopausal women: a randomized-controlled trial. Female pelvic medicine & reconstructive surgery. Conference: 41st annual scientific meeting of the american urogynecologic society 26 (10suppl1): 125	- Conference abstract
Liu, Meichen, Li, Fengyong, Zhou, Yu et al. (2022) Efficacy of CO2 laser treatment in postmenopausal women with vulvovaginal atrophy: A meta-analysis. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 158 (2): 241-251	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Long, Cheng-Yu, Liu, Cheng-Min, Hsu, Shih-Cheng et al. (2006) A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. Menopause 13 (5): 737-743	- Intervention - interventions in the study do not match the review protocol
Lose, G and Englev, E (2000) Oestradiol-releasing vaginal ring versus oestriol vaginal pessaries in the treatment of bothersome lower urinary tract symptoms. BJOG 107 (8ccincontinence): 1029-1034	- Population - study population does not match the review protocol
Melisko, Michelle E, Goldman, Mindy E, Hwang, Jimmy et al. (2017) Vaginal Testosterone Cream vs Estradiol Vaginal Ring for Vaginal Dryness or Decreased Libido in Women Receiving Aromatase Inhibitors for Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA oncology 3 (3): 313-319	- Intervention - interventions in the study do not match the review protocol
Mension, Eduard, Alonso, Inmaculada, Tortajada, Marta et al. (2022) Vaginal laser therapy for genitourinary syndrome of menopause - systematic review. Maturitas 156: 37-59	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Mirkin, Sebastian, Goldstein, Steven R, Archer, David F et al. (2020) Endometrial safety and bleeding profile of a 17beta-estradiol/progesterone oral softgel capsule (TX-001HR). Menopause (New York, N.Y.) 27 (4): 410-417	- Outcome - reported outcomes do not match the review protocol
Mitchell, Caroline M, Guthrie, Katherine A, Larson, Joseph et al. (2019) Sexual frequency and pain in a randomized clinical trial of vaginal estradiol tablets, moisturizer, and placebo in postmenopausal women. Menopause (New York, N.Y.) 26 (8): 816-822	- Trial already included, this publication does not include additional relevant outcome data
Mortensen, Olivia Engholt; Christensen, Sarah Emilie; Lokkegaard, Ellen (2022) The evidence behind the use of LASER for genitourinary syndrome of menopause, vulvovaginal atrophy, urinary incontinence and lichen sclerosus: A state-of-the-art review. Acta obstetricia et gynecologica Scandinavica 101 (6): 657-692	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Najjarzadeh, M., Mohammad Alizadeh Charandabi, S., Mohammadi, M. et al.	- Systematic review.

Study	Code [Reason]
(2019) Comparison of the effect of hyaluronic acid and estrogen on atrophic vaginitis in menopausal women: A systematic review. Post Reproductive Health 25 (2): 100-108	Included studies checked for eligibility and added if relevant for inclusion
Nappi, R E, Panay, N, Bruyniks, N et al. (2015) The clinical relevance of the effect of ospemifene on symptoms of vulvar and vaginal atrophy. Climacteric : the journal of the International Menopause Society 18 (2): 233-40	- Trial already included, this publication does not include additional relevant outcome data
Palacios, S; Ramirez, M; Lilue, M (2022) Efficacy of low-dose vaginal 17beta-estradiol versus vaginal promestriene for vulvovaginal atrophy. Climacteric : the journal of the International Menopause Society 25 (4): 383-387	- Duplicate
Palacios, S; Ramirez, M; Lilue, M (2021) Efficacy of low-dose vaginal 17b-estradiol versus vaginal promestriene for vulvovaginal atrophy. Climacteric	- Outcome - reported outcomes do not match the review protocol
Paraiso, Marie Fidela R, Ferrando, Cecile A, Sokol, Eric R et al. (2020) A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial. Menopause (New York, N.Y.) 27 (1): 50-56	- Comparison - did not include sham laser as a placebo comparator, meaning that effects were likely to be inflated due to failing to blind participants to the allocated intervention
Parnan Emamverdikhan, Aazam, Golmakani, Nahid, Tabassi, Sayyed ASajadi et al. (2016) A survey of the therapeutic effects of Vitamin E suppositories on vaginal atrophy in postmenopausal women. Iranian journal of nursing and midwifery research 21 (5): 475-481	- Outcome - reported outcomes do not match the review protocol
Parsons, Anna, Merritt, Diane, Rosen, Amy et al. (2003) Effect of raloxifene on the response to conjugated estrogen vaginal cream or nonhormonal moisturizers in postmenopausal vaginal atrophy. Obstet. Gynecol. 101 (2): 346-352	- Outcome - reported outcomes do not match the review protocol
Pitsouni, Eleni, Grigoriadis, Themos, Douskos, Athanasios et al. (2018) Efficacy of vaginal therapies alternative to vaginal estrogens on sexual function and orgasm of menopausal women: A systematic review and meta-analysis of randomized controlled trials. European journal of obstetrics, gynecology, and reproductive biology 229: 45-56	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Pitsouni, Eleni, Grigoriadis, Themos, Falagas, Matthew E et al. (2017) Laser therapy for the genitourinary syndrome of menopause. A systematic review and meta-analysis. Maturitas 103: 78-88	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Politano, Carlos A, Costa-Paiva, Lucia, Aguiar, Luiza B et al. (2019) Fractional CO2 laser versus promestriene and lubricant in genitourinary syndrome of menopause: a randomized clinical trial. Menopause (New York, N.Y.) 26 (8): 833-840	- Comparison - did not include sham laser as a placebo comparator, meaning that effects were likely to be inflated due to failing to blind participants to the allocated intervention
Portman, David J, Labrie, Fernand, Archer, David F et al. (2015) Lack of effect of intravaginal dehydroepiandrosterone (DHEA, prasterone) on the endometrium in postmenopausal women. Menopause (New York, N.Y.) 22	- Outcome - reported outcomes do not match the review

Study	Code [Reason]
(12): 1289-95	protocol
Raghunandan, C, Agrawal, S, Dubey, P et al. (2010) A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. Journal of sexual medicine 7 (3ccgynaecologyandfertility): 1284-1290	- Outcome - reported outcomes do not match the review protocol
Reed, Susan D, LaCroix, Andrea Z, Anderson, Garnet L et al. (2020) Lights on MsFLASH: a review of contributions. Menopause (New York, N.Y.) 27 (4): 473-484	- Study design - not a systematic review, randomised controlled trial, or observational study
Rioux, Jacques Emile, Devlin, M Corinne, Gelfand, Morrie M et al. (2018) 17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause (New York, N.Y.) 25 (11): 1208-1213	- Duplicate
Rueda, C, Osorio, A M, Avellaneda, A C et al. (2017) The efficacy and safety of estriol to treat vulvovaginal atrophy in postmenopausal women: a systematic literature review. Climacteric : the journal of the International Menopause Society 20 (4): 321-330	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Sanchez, S.; Baquedano, L.; Mendoza, N. (2021) Treatment of vulvar pain caused by atrophy: A systematic review of clinical studies. Clinical and Experimental Obstetrics and Gynecology 48 (4): 800-805	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Sanchez-Rovira, Pedro, Hirschberg, Angelica Linden, Gil-Gil, Miguel et al. (2020) A Phase II Prospective, Randomized, Double-Blind, Placebo-Controlled and Multicenter Clinical Trial to Assess the Safety of 0.005% Estriol Vaginal Gel in Hormone Receptor-Positive Postmenopausal Women with Early Stage Breast Cancer in Treatment with Aromatase Inhibitor in the Adjuvant Setting. The oncologist 25 (12): e1846-1854	- Outcome - reported outcomes do not match the review protocol
Sarmento, Ayane C A, Lirio, Juliana F, Medeiros, Kleyton S et al. (2021) Physical methods for the treatment of genitourinary syndrome of menopause: A systematic review. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 153 (2): 200-219	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Scheffers, Carola S, Armstrong, Sarah, Cantineau, Astrid E P et al. (2015) Dehydroepiandrosterone for women in the peri- or postmenopausal phase. The Cochrane database of systematic reviews 1: cd011066	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Seyyedi, Fatemeh; Kopaei, Mahmoud Rafiean; Miraj, Sepideh (2016) Comparison between vaginal royal jelly and vaginal estrogen effects on quality of life and vaginal atrophy in postmenopausal women: a clinical trial study. Electronic physician 8 (11): 3184-3192	- Outcome - reported outcomes do not match the review protocol
Seyyedi, Fatemeh; Rafiean-Kopaei, Mahmoud; Miraj, Sepideh (2016) Comparison of the Effects of Vaginal Royal Jelly and Vaginal Estrogen on Quality of Life, Sexual and Urinary Function in Postmenopausal Women. Journal of clinical and diagnostic research : JCDR 10 (5): qc01-5	- Outcome - reported outcomes do not match the review protocol
Simon, J A, Kagan, R, Archer, D F et al. (2019) TX-004HR clinically improves symptoms of vulvar and vaginal atrophy in postmenopausal women. Climacteric : the journal of the International Menopause Society 22 (4): 412-418	- Duplicate
Simon, J, Goldstein, I, Goldstein, S et al. (2019) Phase III Study Evaluating Efficacy and Safety of Ospemifene in Menopausal Women with Moderate to Severe Vaginal Dryness: overall Patient Satisfaction with Treatment. Journal	- Conference abstract

Study	Code [Reason]
of sexual medicine. Conference: ISSWSH/ISSM joint meeting, 'it takes 2 to tango'. United states 16suppl3 (6): 35	
Simon, James A, Altomare, Corrado, Cort, Susannah et al. (2018) Overall Safety of Ospemifene in Postmenopausal Women from Placebo-Controlled Phase 2 and 3 Trials. Journal of women's health (2002) 27 (1): 14-23	- Outcome - reported outcomes do not match the review protocol
Simon, James A, Archer, David F, Kagan, Risa et al. (2017) Visual improvements in vaginal mucosa correlate with symptoms of VVA: data from a double-blind, placebo-controlled trial. Menopause 24 (9): 1003-1010	- Outcome - reported outcomes do not match the review protocol
Simon, James A, Lin, Vivian H, Radovich, Cathy et al. (2013) One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 20 (4): 418-427	- Outcome - reported outcomes do not match the review protocol
Speroff, L (2003) Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. Obstetrics and gynecology 102 (4ccgynaecologyandfertilityccincontinence): 823-834	- Intervention - interventions in the study do not match the review protocol
Srinivasan, Sujatha, Hua, Xing, Wu, Michael C et al. (2022) Impact of Topical Interventions on the Vaginal Microbiota and Metabolome in Postmenopausal Women: A Secondary Analysis of a Randomized Clinical Trial. JAMA network open 5 (3): e225032	- Outcome - reported outcomes do not match the review protocol
Stute, Petra (2013) Is vaginal hyaluronic acid as effective as vaginal estriol for vaginal dryness relief?. Arch. Gynecol. Obstet. 288 (6): 1199-1201	- Study design - not a systematic review, randomised controlled trial, or observational study
Suwanvesh, Narathorn, Manonai, Jittima, Sophonsritsuk, Areepan et al. (2017) Comparison of Pueraria mirifica gel and conjugated equine estrogen cream effects on vaginal health in postmenopausal women. Menopause 24 (2): 210-215	- Intervention - interventions in the study do not match the review protocol
Weidlinger, S, Schmutz, C, Janka, H et al. (2021) Sustainability of vaginal estrogens for genitourinary syndrome of menopause - a systematic review. Climacteric : the journal of the International Menopause Society 24 (6): 551-559	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion
Zhang, Guo-Qiang, Chen, Jin-Liang, Luo, Ying et al. (2021) Menopausal hormone therapy and women's health: An umbrella review. PLoS medicine 18 (8): e1003731	- Systematic review. Included studies checked for eligibility and added if relevant for inclusion

Excluded economic studies

No economic evidence was identified for this review. See Supplement 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

K.1.1 Research recommendation

What is the safety, efficacy, and cost effectiveness of vaginal laser for genitourinary symptoms associated with menopause?

Why this is important

There are few effective non-hormonal options for women with genitourinary symptoms associated with menopause. Preliminary evidence suggests that vaginal laser may be effective, but this requires confirmation in larger trials comparing vaginal laser with sham laser and with vaginal oestrogen (gold standard). The cost effectiveness of vaginal laser is also uncertain.

Rationale for research recommendation

Table 30: Research recommendation rationale

Importance to 'patients' or the population	Further research on the safety, efficacy, and cost effectiveness of laser treatment for genitourinary symptoms associated with menopause would provide greater certainty about their use, potentially leading to important additional treatments being made available to women for what is often a distressing condition.
Relevance to NICE guidance	This evidence would be essential to inform future updates of recommendations in the current guideline to enable evidence-based recommendations about vaginal laser for genitourinary symptoms associated with menopause.
Relevance to the NHS	This research would provide an evidence base on the safety and effectiveness of vaginal laser and could affect the types of treatment provided by the NHS to menopausal women with genitourinary symptoms.
National priorities	This research is relevant to the government's women's health strategy which aims to improve the health of women everywhere over the next 10-years, and specifically addresses the following sections on menopause: • healthcare professionals in primary care are well informed about the menopause, and able to offer women evidence-based advice and treatment options, including HRT and alternatives • there is increased research into the menopause, including different treatment

	options and impacts of menopause or menopause treatment on future health risks
Current evidence base	The current evidence suggests that vaginal laser could be an effective treatment for dyspareunia and vulvovaginal dryness associated with menopause compared to alternative treatments. There is also evidence that it could be a cost-effective intervention under more favourable effectiveness estimates. However, the evidence is based on a small number of studies with low numbers of participants and consequently there are wide, imprecise credible intervals. The uncertainty around the evidence could be resolved with larger randomised controlled trials that should be able to address these issues.
Equality considerations	Further research would address equality considerations particularly in the following groups, people: • with disabilities • from diverse races and ethnicities • from diverse socio-economic backgrounds

NHS: national health service

Modified PICO table

Table 31: Research recommendation modified PICO table

Population	Women, trans men, and non-binary people registered female at birth (who are not taking cross sex hormones as gender affirming therapy) with genitourinary symptoms associated with menopause (including perimenopause and postmenopause). The committee further recommends research that would address equality considerations in the equality impact assessment form, particularly in the following groups, people: • with disabilities • across a range of race / ethnicities • from a wider range of socio-economic backgrounds
Intervention	• Vaginal lasers
Comparator	• Placebo or sham treatment • No treatment
Outcome	• Pain with sex • Vulvovaginal symptoms (dryness, discomfort, or irritation) • Discomfort or pain when urinating • Discontinuation of treatment due to side effects • Distress, bother or interference of genitourinary symptoms • Satisfaction with treatment • Cost effectiveness of treatment
Study design	Randomised controlled trials

Timeframe	5 years
Additional information	None

PICO: population, intervention, comparator, outcome

K.1.2 Research recommendation

What is the long-term (beyond 12 months) safety of vaginal oestrogens when use in women with genitourinary symptoms associated with menopause?

Why this is important

Vaginal oestrogens are currently used long-term (>12 months) for genitourinary symptoms associated with menopause which may be persistent. However, evidence for long-term safety and efficacy is lacking.

Rationale for research recommendation

Table 32: Research recommendation rationale

Importance to 'patients' or the population	Genitourinary symptoms associated with menopause are often persistent and return when treatment is stopped. As a result, vaginal oestrogens are commonly prescribed beyond 12 months. It is important to know the risks of vaginal oestrogens for women who wish to continue their use long term, however the evidence on long-term use is limited. Further research may alter the advice and counselling given to women when prescribing vaginal oestrogens and provide greater confidence amongst clinicians and symptomatic women about their long-term use.
Relevance to NICE guidance	There was limited evidence on the safety of vaginal oestrogens for genitourinary symptoms in menopausal women particularly when used in the long-term (beyond 12 months). Research in this area is essential to inform future updates of key recommendations in the guidance.
Relevance to the NHS	This research would provide an evidence base on the use of vaginal oestrogens which could impact whether vaginal oestrogen can be offered for long-term use (more than 12months) by the NHS in women with genitourinary symptoms associated with menopause.
National priorities	This research is relevant to the government's women's health strategy which aims to improve the health of women everywhere over the next 10-years, and specifically addresses the following sections on menopause: • healthcare professionals in primary care are well informed about the menopause, and able to offer women evidence-based advice and treatment options, including HRT and alternatives • there is increased research into the menopause, including different treatment options and impacts of menopause or

	menopause treatment on future health risks
Current evidence base	There was minimal evidence available of low to very low quality from observational studies only and these did not include a long-term follow-up.
Equality considerations	Further research would address equality considerations particularly in the following groups, people: • with disabilities • from diverse races and ethnicities • from diverse socio-economic backgrounds

HRT: hormonal replacement therapy; NHS: national health service

Modified PICO table

Table 33: Research recommendation modified PICO table

Population	Women, trans men, and non-binary people registered female at birth (who are not taking cross sex hormones as gender affirming therapy) with genitourinary symptoms associated with menopause (including perimenopause and postmenopause). The committee further recommends research that would address equality considerations in the equality impact assessment form, particularly in the following groups, people: • with disabilities • across a range of race / ethnicities • from a wider range of socio-economic backgrounds
Intervention	• Vaginal oestrogen ○ Estriol cream ○ Estriol pessary ○ Estriol gel ○ Estradiol vaginal tablet ○ Estradiol ring
Comparator	• Placebo treatment (including non-hormonal treatment such as moisturisers and lubricants) • No treatment • Sham treatment
Outcome	• Death from any cause • Venous thromboembolism • Cardiovascular disease • Type 2 diabetes • Incidence of breast cancer • Incidence of endometrial cancer • Incidence of ovarian cancer
Study design	Randomised controlled trials and non-randomised comparative studies
Timeframe	5 years (12 months minimum follow-up)
Additional information	None

PICO: population, intervention, comparator, outcome.

1

Appendix L Network meta-analysis report from the NICE Guidelines Technical Support Unit (TSU)

Network meta-analysis report for review question: What is the effectiveness of treatments such as local oestrogen, ospemifene, prasterone and transvaginal laser therapy for managing genitourinary symptoms associated with the menopause?

Prepared by: NICE Guidelines TSU, Bristol (Hugo Pedder, Beatrice Downing and Nicky J. Welton)

Introduction

The purpose of this analysis was to estimate the comparative effectiveness of various interventions for treating genitourinary symptoms in menopausal women. In total 39 studies were included in these analyses comparing 21 interventions (or combinations of interventions) and 11 classes of intervention.

The outcomes analysed were pain during/after sex (dyspareunia), vulvovaginal dryness (dryness), vulvovaginal discomfort/irritation (discomfort), pain/discomfort when urinating (dysuria) and discontinuation due to adverse events. The SMD measure of effect was used to combine evidence from studies reporting efficacy in terms of a continuous measurement on various genitourinary symptom scales for dyspareunia, dryness, discomfort and dysuria. Results for these outcomes are back-transformed to a 0-3 symptom scale (lower scores are better).

Methods

Network meta-analysis

In order to take all trial information into consideration network meta-analyses (NMA) were conducted. NMA is a generalisation of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials[1–3]. A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A versus B trial, is the same as the relative effect between A and B estimated indirectly from A versus C and B versus C trials. NMA techniques strengthen inference concerning the relative effect of two treatments by including both direct and indirect comparisons between treatments, and, at the same time, allow simultaneous inference on all treatments while respecting randomisation[2,3].

Simultaneous inference on the relative effects of all treatments is possible whenever treatments are part of a single “network of evidence”, that is, every treatment is linked to at least one of the other treatments under assessment. The correlation between the random effects of multi-arm trials (i.e. those with more than 2 arms) in the network is taken into account in the analysis[1(p2)]. In a NMA we assume that intervention A is similar (in dose, administration etc.) when it appears in the A *v* B and A *v* C studies and also that every patient included the network could have been assigned to any of the interventions[3]– a concept called ‘joint randomisability’[4].

A Bayesian framework is used to estimate all parameters, using Markov chain Monte Carlo simulation methods implemented in WinBUGS 1.4.3[5,6]. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic[7] and was satisfactory by 50,000 simulations for all outcomes[8]. A further simulation sample of at least 20,000 iterations post-convergence was

obtained on which all reported results were based. Sample WinBUGS code is provided in Supplement 2.

For binary data (discontinuation due to adverse events), studies with zero or 100% events in all arms were excluded from the analysis because these studies provide no evidence on relative effects[1]. For studies with zero or 100% events in one arm only, we planned to analyse the data without continuity corrections where computationally possible. Where this was not possible, we used a continuity correction where we added 0.5 to both the number of events and the number of non-events, which has shown to perform well when there is an approximate 1:1 randomisation ratio across intervention arms[9]. For the small number of studies in which there was not an approximate 1:1 randomisation ratio, a continuity correction that was weighted by the reciprocal of the opposite group arm size[9].

Reporting of results

Network diagrams are presented for each population and outcome. The edges (lines) connecting each pair of interventions represent a direct comparison.

Relative intervention effects are reported in the *"Effect size vs Reference"* worksheets of Supplements 9 to 16 as posterior median log-odds ratios (log-OR) or mean differences (MD) back-transformed from standardised mean differences (SMD) and 95% Credible Intervals (CrIs) compared to Inactive placebo treatment. The full list of ORs and MDs for each intervention and class compared to every other are reported in the *"Treatment Direct Effects"* or *"Class Direct Effects"* worksheets of Supplements 9 to 16.

We also report posterior mean rank of each class, along with the posterior median and 95% CrIs, with the convention that the lower the rank the better the class. These can be found in the *"Ranks"* worksheet of Supplements 9 to 16.

NMA methodology

Likelihood and link functions

Following the approach described in NICE Technical Support Document 2[1], data are modelled using a likelihood and a link function that relates the data to the fitted model values, θ_{ik} .

With continuous outcome data, meta-analysis is usually based on the sample means, with standard errors assumed known. Here we are interested in modelling the mean changes from baseline, which are assumed to be approximately normally distributed, with likelihood

$$y_{C,ik} \sim N\left(\theta_{ik}, se^2_{C,ik}\right)$$

An identity link function is used such that the fitted model value θ_{ik} is the mean of this distribution.

For binary outcomes, the data used are the number of responders and the total number of participants (either at randomisation or those who completed depending on the type of analysis). These are modelled using a binomial likelihood

$$r_{ik} \sim Binomial(p_{ik}, n_{ik})$$

This is typically modelled using a logit link function, $\theta_{ik} = \text{logit}(p_{ik})$. However, where binary data are reported at different follow-up times in different trials, a cloglog link function can be used to assume an underlying Poisson process for each trial arm, with a constant event rate that takes into account the different follow-up times[1]

$$\theta_{ik} = \text{cloglog}(p_{ik}) = \log(f_i) + \mu_i + \delta_{ik}$$

where f_i is the follow-up time in study i.

NMA model

For a random effects model we write

$$\theta_{ik} = \gamma_i + \delta_{ik} \quad (1)$$

where γ_i are the trial-specific effects of the treatment in arm 1 of trial *i*, treated as unrelated nuisance parameters, and the δ_{ik} are the trial-specific treatment effects of the treatment in arm *k* relative to the treatment in arm 1 in that trial, where $\delta_{i1} = 0$. The trial-specific random effects δ_{ik}, represent the mean differences between the change from baseline for the treatment in arm *k* and the treatment in arm 1 of trial *i* and, in a random effects model,

$$\delta_{ik} \sim \text{Normal}(d_{t_{i1},t_{ik}}, \sigma^2) \quad (2)$$

where σ^2 denotes the between-study heterogeneity, assumed common to all treatment comparisons and $d_{t_{i1}t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$ are the pooled mean differences, defined by the consistency equations ($d_{11} = 0$). The fixed effect model is obtained by replacing equation (1) with $\theta_{ik} = \gamma_i + d_{1,t_{ik}} - d_{1,t_{i1}}$. Where studies with more than 2 arms are present, a correlation is induced in the trial specific effects δ_{ik} so equation (2) is replaced by a multivariate normal distribution with correlation equal to 0.5[1,10].

Prior distributions and computation

In this case non-informative prior distributions are chosen for the pooled treatment effects, relative to treatment 1, d_{1k}, k=2,…,nt , where nt is the number of treatments in the network

$$d_{1k} \sim \text{Normal}(0, 100^2) \quad (3)$$

and a Uniform prior between 0 and 4 is chosen for the between-study heterogeneity, which is thought to be sufficiently wide to capture the variability in difference in mean change from baseline across trials making the same comparisons.

Class models

Interventions were grouped into classes shown in Table 34, though several interventions were not explored in any studies that were included in final analyses and were consequently not included in the NMAs. The protocol allowed for combinations of the interventions listed below.

Table 34. Table of interventions and classes included in the protocol.

Intervention	Class
Estriol cream	Estriol
Estriol pessary	
Estriol pessary 0.3mg	
Estriol pessary 0.4mg	
Estriol pessary 0.5mg	
Estriol pessary 1.0mg	
Estriol gel	
Estradiol vaginal tablet/pessary	Estradiol
Estradiol ring	
Estradiol gel	
Estradiol cream	
Estradiol softgel capsule	
Conjugated estrogen tablet	Conjugated estrogen
Conjugated estrogen cream	
Ospemifene	Selective estrogen receptor modulator (SERM)
Prasterone	Dehydroepiandrosterone (DHEA)
CO2 Laser	Laser
Erbium Laser	
Moisturiser	Local treatment
Lubricant	
Placebo	Inactive

Classes of treatments are groups of interventions which are thought to have similar effects. Class models were used so that strength could be borrowed across treatments in the same class and to reconnect disconnected networks. For all networks with at least three treatments within any class, fixed and random class effect models were compared. Random class effect models assume that the effects of treatments in a class are distributed around a common class mean with a within-class variance.

The pooled relative treatment effects specified in equation (2) are assumed to be exchangeable within class:

$$d_{1,k} \sim N\left(m_{D_k}, \tau^2_{D_k}\right)$$

Where D_k indicates the class to which treatment k belongs. Given limited available data to estimate class-specific variances, τ_{D_k} were assumed to be equal across the network such that $\tau_{D_k} = \tau_{class}$.

For networks with no more than two treatments within any class, only fixed class models were fitted due to difficulties in estimating the class variance. Fixed class effect models assume within-class variance equal to zero ($\tau^2_{class} = 0$), such that the treatment effects within a class are all equal.

The within-class mean treatment effects were given vague priors $\mu_i \sim N(0,100^2)$ and the within-class standard deviation (SD) was given a vague uniform prior of $\tau_{class} \sim U(0,5)$ for

binary outcomes and $\tau_{class} \sim U(0,4)$ to reflect the slightly narrower range of plausible values for continuous outcomes modelled as SMDs.

Random class models provide estimates of both intervention effects and class effects, whereas for the fixed class models these are assumed equal so only class effects are reported in this document, with intervention effects shown in forest plots in Appendix E and in Supplement 8.

Model fit and inconsistency checking

Model fit

Goodness of fit was measured using the posterior mean of the residual deviance, which is a measure of the magnitude of the difference between the observed data and their model predictions[11]. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points. We also report the Deviance Information Criterion (DIC) which penalises model fit with model complexity[11]. Finally, we report the between studies standard deviation (heterogeneity parameter) to assess the degree of statistical heterogeneity. If the inconsistency model had the smallest posterior mean residual deviance or heterogeneity then this indicated potential inconsistency in the data. In comparing models, differences of ≥5 points for posterior mean residual deviance and DIC were considered meaningful[11], with lower values being favoured.

Inconsistency checking

Consistency between the different sources of indirect and direct evidence was explored statistically by comparing the fit of a model assuming consistency with a model which allowed for inconsistency (also known as an unrelated mean effect model) at the treatment-level, whilst still modelling class effects. Sample WinBUGS code for the inconsistency model is provided in Supplement 5. To explore whether specific data points are contributing to inconsistency we plot dev-dev plots that compare the contribution to the residual deviance under the inconsistency model against the consistency model. Data-points that fit much better under the inconsistency model indicate potential inconsistency that can be explored further by a comparison of direct and indirect estimates.

In standard NMA, node-splitting is used to estimate direct and indirect estimates, however this cannot be straightforwardly applied for class effect NMA models. Instead, we use an approximation approach as a heuristic to identify comparisons in which direct and indirect evidence are likely to strongly disagree.

Direct estimates from the unrelated mean effect model are reported in the separate spreadsheets of results for each outcome, and these can be compared to NMA estimates from the consistency models. To identify comparisons for which there was likely to be a discrepancy between direct and indirect estimates, we estimated the indirect evidence contributions by subtracting the direct evidence contributions estimated using the unrelated mean effects model from the NMA estimates estimated using the consistency model, assuming normality of the posterior distributions:

$$d_{ind} = \frac{d_{nma}(w_{dir} + w_{ind}) - w_{dir} d_{dir}}{w_{ind}}$$

Where d_{ind} is the indirect relative effect, d_{nma} is the mixed relative effect estimated from the NMA, d_{dir} is the direct relative effect estimated from the inconsistency model, for a given treatment comparison. w_{nma}, w_{dir} and w_{ind} are the inverse-variance weights, calculated as

$\frac{1}{\sigma_{nma}^2}$, $\frac{1}{\sigma_{dir}^2}$ and $\frac{1}{\sigma_{ind}^2}$ for the mixed, direct and indirect effects respectively. σ_{nma} and σ_{dir} are the standard deviations of the posterior distributions for the corresponding relative effects. σ_{ind} is the standard error for the indirect relative effect, calculated as:

$$\sigma_{ind} = \sqrt{\frac{\sigma_{nma}^2 \sigma_{dir}^2}{\sigma_{dir}^2 - \sigma_{nma}^2}}$$

The difference between direct and indirect estimates can then be estimated, and a Wald test (with a rejection threshold of 0.05) can be used to test whether direct and indirect evidence are in agreement.

SMD analysis: methods

We wished to include as many trials and information as possible in each analysis even when data were reported in different ways. For continuous outcomes (dyspareunia, dryness, discomfort and dysuria) this meant analysis using Standardised Mean Differences (SMDs). For the SMD analysis we wanted to conduct a NMA on the mean difference in change from baseline (CFB) (for which standard methods are available)[1]. The data required for each arm of each study are the mean CFB, the standard deviation in CFB and the total number of individuals in that arm (or the standard error of the mean change from baseline).

Several studies reported medians and interquartile ranges (IQR), and these were transformed to means and SDs using the Box-Cox method[12] or, if the IQR was bounded by zero, the quantile estimation method[13].

As the methods noted above for analysis of data with normal likelihood are study and arm specific, they apply regardless of which scale was used in that trial. However, pooling of the difference in means across different scales is not appropriate. A common approach is to use the SMD, where the mean difference is divided by a standardising constant, which can be the population standard deviation for each scale (if known). As the population standard deviations for genitourinary symptom scales are unknown these were estimated from the data to create an internal reference standard deviation for each scale[14]. The use of internal reference standard deviations limits the impact of outlying study-specific standard deviations on treatment effects. The reference standard deviation for each scale, was estimated by pooling study-specific standard deviations at baseline, weighting this by the sample size of each study.

The SMD for arm *k* of study *i* compared to arm 1 of study i, λ_{ik}, is given as

$$\lambda_{ik} = \frac{y_{ik} - y_{i1}}{s_{scale_i}} \quad (4)$$

where s_{scale_i} is the standard deviation in of the scale reported in study i.

The likelihood for each study reporting the various outcomes are as before, but the parameter of interest is now the SMD λ_{ik}. Thus the model is defined as

$$\lambda_{ik} = \gamma_i + \delta_{ik} \quad (5)$$

This model is linked to the mean change from baseline through the following relationship

$$\theta_{ik} = \lambda_{ik} s_{scale} \quad (6)$$

Prior distributions can be defined as before.

Intention-to-treat (ITT)

Intention-to-treat results were used where reported. However, since many studies only reported results for those who completed the study, these results were also synthesised if the dropout rate was less than 10%, meaning that the impact of attrition bias would be limited. The impact of this was explored in post-hoc sensitivity analyses.

Pre-specified sensitivity analyses

As a pre-specified sensitivity analysis we evaluated the potential for small study bias using the methods of Dias et al. (2010)[15]. Bias was assumed in comparisons of active interventions vs inactive control, and no bias assumed between inactive control comparisons, as well as active intervention comparisons.

Bias-adjusted models were compared to base-case consistency models using DIC. If the bias-adjusted model had a DIC that was lower by ≥5 then results from this were reported over the unadjusted model[11].

For Standardised Mean Differences, the impact of study follow-up was also investigated as a further sensitivity analysis, using data from studies reporting outcomes at 2-12 weeks follow-up.

Key additional assumptions made within the analyses

- We assumed the existence of class effects and modelled the data in this way. Although we investigated assuming individual interventions were similar and exchangeable within a class, this model added complexity that the data did not support. Results indicated that intervention effects within a class were typically extremely similar, and thus (based on model selection using DIC) we report fixed class effect models for all outcomes.
- For genitourinary symptoms we assumed that study duration was not an effect odifier, which implies that mean differences are the same at 2 weeks as they are at 52 weeks follow-up. This is a strong assumption that may be difficult to justify clinically, but there were insufficient data to separately explore effects at longer follow-up that were needed to inform the economic model. We explored the impact of this assumption in the sensitivity analyses section of this appendix.
- We assumed additivity of Local treatment (Moisturiser or Lubricant) efficacy when given in combination with other treatments. This meant that if Local treatment was given with other treatments in all arms in a study, we assumed that the relative effects of the different treatments in each arm would be the same as in a similar study in which Local treatment was not given in any arms (i.e. the Local treatment effect cancels out when comparing the two arms).
- For estimating the indirect evidence contributions from inconsistency models we assumed that the posterior distributions of relative effects were normally distributed. Whilst they were generally approximately normal, deviations from normality in some cases may have affected our findings regarding which comparisons had significant discrepancies between direct and indirect evidence.

Results

3 studies investigating CO2 laser (Paraiso 2020, Politano 2019, Eftekhar 2020) were excluded because they did not include sham laser as a placebo comparator, meaning that

effects were likely to be inflated due to failing to blind participants to the allocated intervention.

Outcome: Pain during/after sex (Dyspareunia)

24 trials were included, all of which reported CFB. These compared 16 interventions and 10 classes (Table 35, Figure 17, Figure 18).

The following internal reference standard deviations[14] were estimated for the following scales, and these were used for standardization when estimating SMDs:

- 4-point scale (0-3): 0.673
- tFSFI - transformed FSFI pain domain (0-6): 2.700
- VAS scale (0-10): 2.679
- 5-point scale (0-4): 1.171

A fixed class effects model was selected based on DIC (Table 1 in Supplement 6).

Although DIC was similar for the NMA and inconsistency models, between-study heterogeneity was lower, suggesting possible inconsistency. The dev-dev plot (Figure 19) suggests that this is caused by the inclusion of Mitchell 2018, which compared Oestradiol (tablet) + Placebo gel versus Placebo tablet + Moisturiser (Replens) versus Placebo tablet + Placebo gel (Figure 19). In this study, Placebo tablet + Placebo gel appeared to be similarly as effective as Oestradiol (tablet) + Placebo gel, and better than Placebo tablet + Moisturiser (Replens), a result which was inconsistent with other studies in the network and is clinically unlikely. Exclusion of this study from the network resolved the inconsistency and improved model fit. However, we have included it in analyses based on both the committee's preference and because there were no concerns regarding the conduct of the trial.

There was no evidence of bias due to small study effects, performed as a prespecified sensitivity analysis (Table 1 in Supplement 6). Further details are given in the sensitivity analyses section of this appendix. Reported results are therefore based on the random-effects fixed class NMA model assuming consistency and can be found in Supplement 16.

Moderate between trials heterogeneity was found relative to the size of the intervention

effect estimates ($\tau = 0.40$ (95% CrI 0.24, 0.63)). Relative effects are presented compared to Placebo (Figure 20).

Table 35. Table of interventions, classes and number of patients (N) included in Dyspareunia analysis.

	Intervention	N	Class	N
1	Placebo	2293	Inactive	2293
2	Prasterone	618	DHEA	618
3	Co2 laser	88	Laser	88
4	Co2 laser + estriol cream	15	Laser + vaginal estrogen	15
5	Moisturiser	247	Local tx	327
6	Lubricant	80		
7	Levonorgestrel estradiol tablet	20	Progestin + vaginal estrogen	20
8	Ospemifene	892	SERM	892
9	Estriol cream	100	Estriol	150
10	Estriol gel	50		
11	Estradiol tablet	177	Estradiol	736
12	Estradiol gel	40		

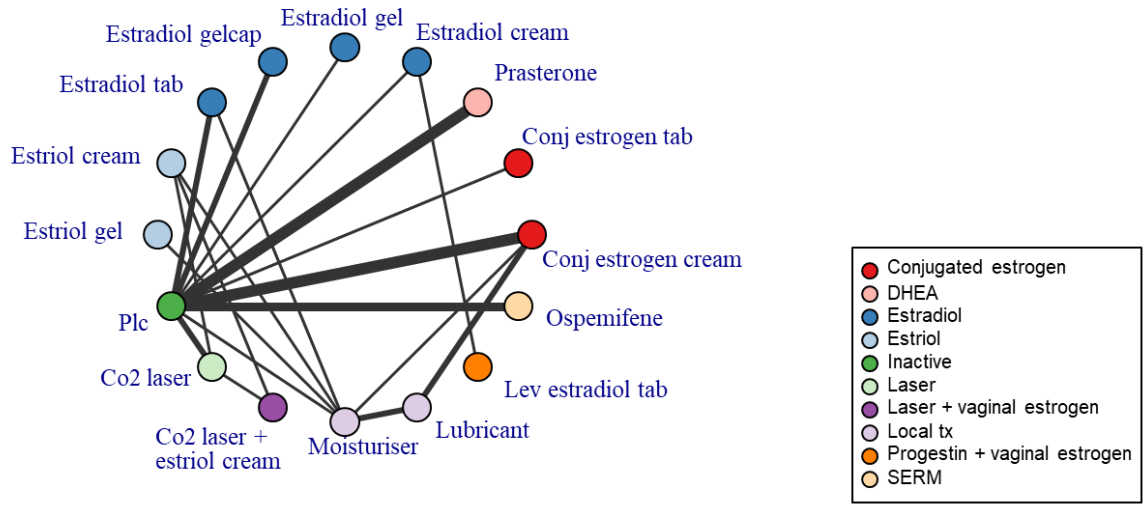
	Intervention	N	Class	N
13	Estradiol cream	307		
14	Estradiol softgel capsule	212		
15	Conjugated estrogen tablet	34	Conjugated estrogen	370
16	Conjugated estrogen cream	336		

4

5

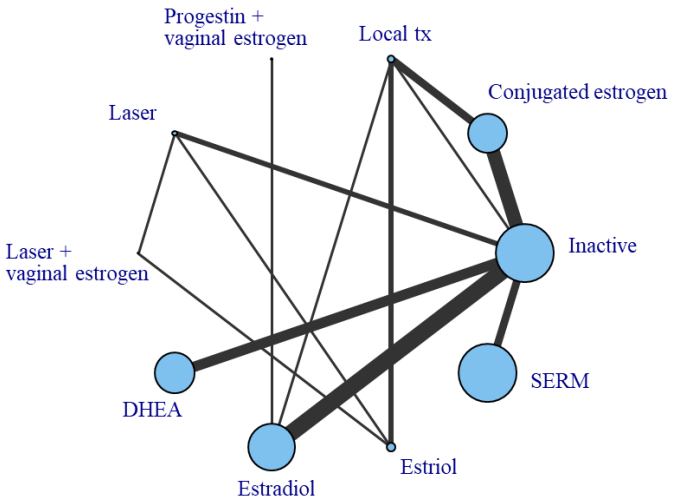
6

7 **Figure 17: Network diagram of all studies included in analysis by intervention.**
8 **Dyspareunia.**



9

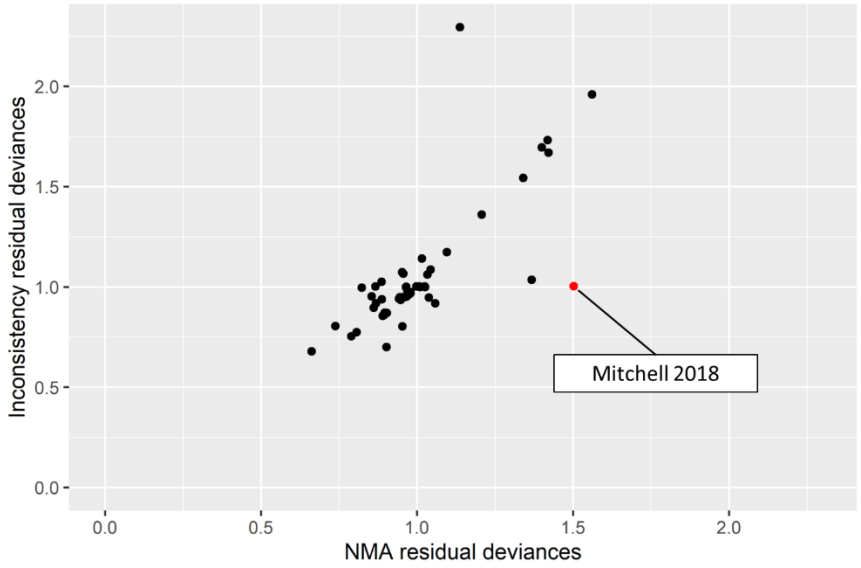
10 **Figure 18: Network diagram of all studies included in analysis by class. Dyspareunia.**



11

12

Figure 19: Dev-dev plot. Dyspareunia.



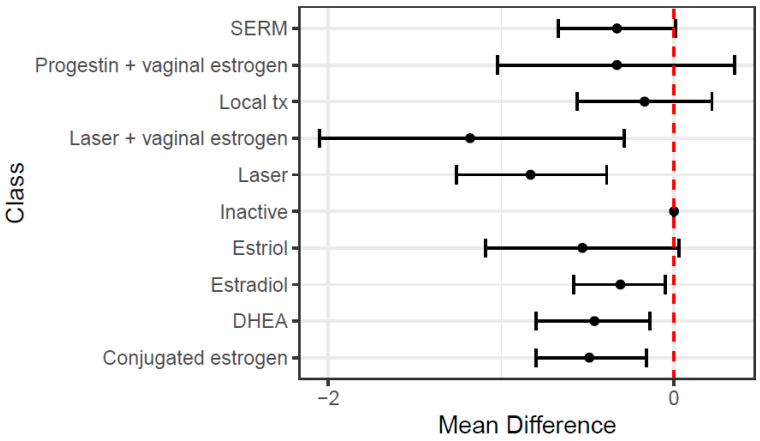
The classes for which there is clear evidence suggesting decreased dyspareunia compared to Placebo are the following (Figure 20):

- DHEA
- Laser
- Laser + vaginal estrogen
- SERM
- Estriol
- Oestradiol
- Conjugated estrogen

There is evidence of a decreased dyspareunia (lower MD corresponds to improved outcomes) compared to Placebo for the following interventions. (Figure 20)

- Prasterone
- CO2 laser
- CO2 laser + Estriol cream
- Ospemifene
- Estriol cream
- Estriol gel
- Oestradiol tablet
- Oestradiol gel
- Oestradiol cream
- Oestradiol softgel capsule
- Conjugated estrogen tablet
- Conjugated estrogen cream

Figure 20: Class level dyspareunia. Mean Differences (MD) and 95% credible intervals for every class compared to Inactive (reported on 4-point 0-3 dyspareunia scale). MD < 0 imply a reduction in dyspareunia compared to Inactive.



Mean Difference	95%CrI
−0.33	(−0.67, 0.01)
−0.33	(−1.02, 0.35)
−0.17	(−0.56, 0.22)
−1.18	(−2.05, −0.29)
−0.83	(−1.26, −0.39)
0.00	Reference
−0.53	(−1.09, 0.03)
−0.31	(−0.58, −0.05)
−0.46	(−0.8, −0.14)
−0.49	(−0.8, −0.16)

Laser + vaginal estrogen and Laser are the highest ranked classes with posterior median ranks of 1st (95% CrI 1st to 6th) and 2nd (95% CrI 1st to 5th) respectively (Supplement 16, *"Ranks"* worksheet). However, these classes were investigated on small numbers of patients (15 and 88 respectively in total), which limits the ability to draw strong conclusions on them.

The lowest ranked class is Inactive (placebo) at 10th (95% CrI 8th to 10th), and the lowest ranked active class is Local treatment (8th, 95% CrI 5th to 10th) (Table 36).

Table 36. Posterior median rank and 95% credible intervals by class. Dyspareunia.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Laser + vaginal estrogen	1.56	1 (1, 6)
Laser	2.31	2 (1, 5)
Estriol	4.53	4 (2, 9)
Conjugated estrogen	4.67	4 (2, 8)
DHEA	4.96	5 (2, 9)
Progestin + vaginal estrogen	6.30	7 (1, 10)
SERM	6.36	6 (3, 9)
Estradiol	6.68	7 (3, 9)
Local tx	8.06	8 (5, 10)
Inactive	9.57	10 (8, 10)

Outcome: Vulvovaginal dryness (Dryness)

25 trials were included, all of which reported CFB. These compared 17 interventions and 10 classes (Table 37, Figure 21, Figure 22).

The following internal reference standard deviations[14] were estimated for the following scales, and these were used for standardization when estimating SMDs:

- 4-point scale (0-3): 0.580
- tFSFI - transformed FSFI pain domain (0-6): 3.194
- VAS scale (0-10): 2.208
- 5-point scale (0-4): 0.595

A fixed class effects model was selected based on DIC (Table 2 in Supplement 6).

There was no evidence of inconsistency (Figure 23). DIC was higher in the inconsistency model than the NMA model, and between-study heterogeneity was similar. One study, Hirschberg 2020, had high deviance in both models as it reported a substantially greater treatment effect for Oestradiol gel versus Moisturiser than was found in other studies in the network.

There was no evidence that incorporating bias-adjustment for small study effects (performed as a prespecified sensitivity analysis) improved model fit or reduced between-study heterogeneity. Further details are given in the sensitivity analyses section of this appendix. Reported results are therefore based on the random-effects fixed class NMA model assuming consistency and can be found in Supplement 14.

Moderate between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau = 0.36$ (95% CrI 0.23, 0.57)). Relative effects are presented compared to Placebo.

Table 37. Table of interventions, classes and number of patients (N) included in Dryness analysis.

	Intervention	N	Class	N
1	Plc	2145	Inactive	2145
2	Prasterone	618	DHEA	618
3	Co2 laser	88	Laser	88
4	Co2 laser + estriol cream	15	Laser + vaginal estrogen	15
5	Moisturiser	160	Local tx	312
6	Lubricant	152		
7	Lev estradiol tab	20	Progestin + vaginal estrogen	20
8	Ospemifene	749	SERM	749
9	Estriol cream	87	Estriol	185
10	Estriol pess 50	48		
11	Estriol gel	50		
12	Estradiol tab	225	Estradiol	784
13	Estradiol gel	40		
14	Estradiol cream	307		
15	Estradiol gelcap	212		
16	Conj estrogen tab	34	Conjugated estrogen	370
17	Conj estrogen cream	336		

Figure 21: Network diagram of all studies included in analysis by intervention. Dryness.

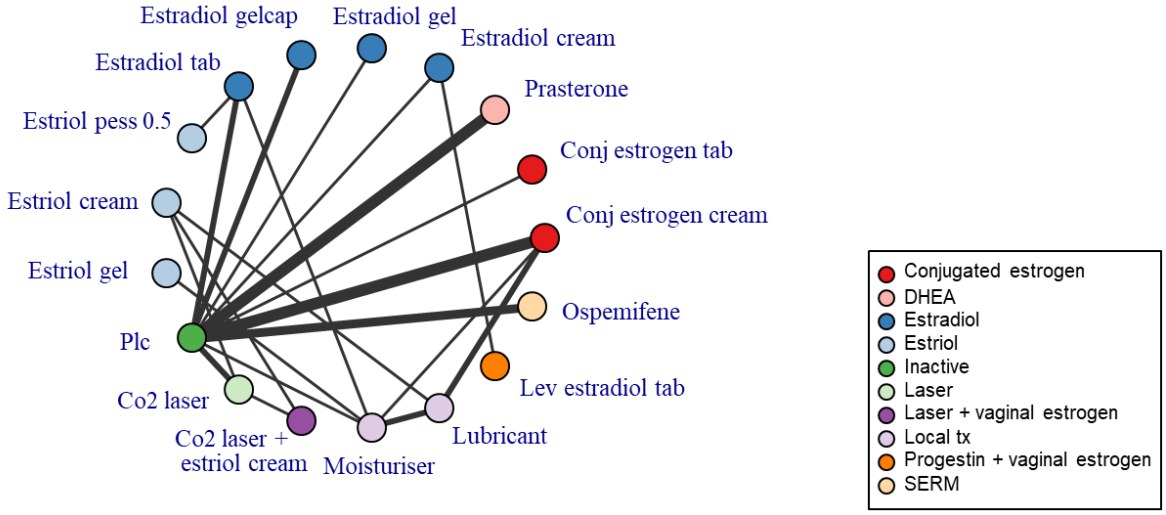


Figure 22: Network diagram of all studies included in analysis by class. Dryness.

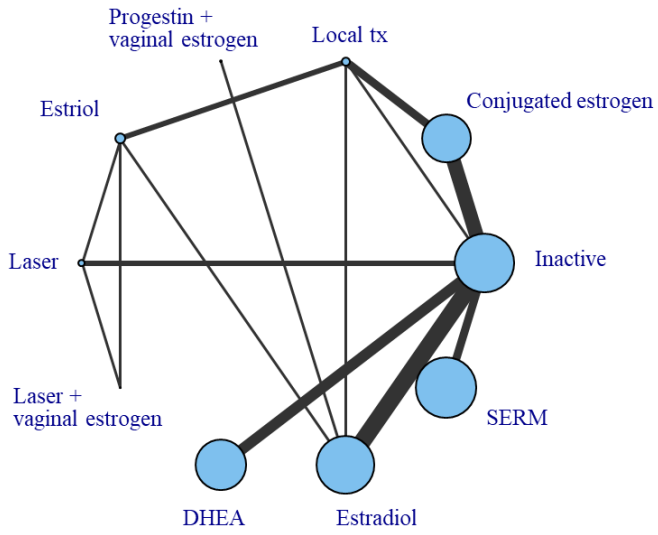
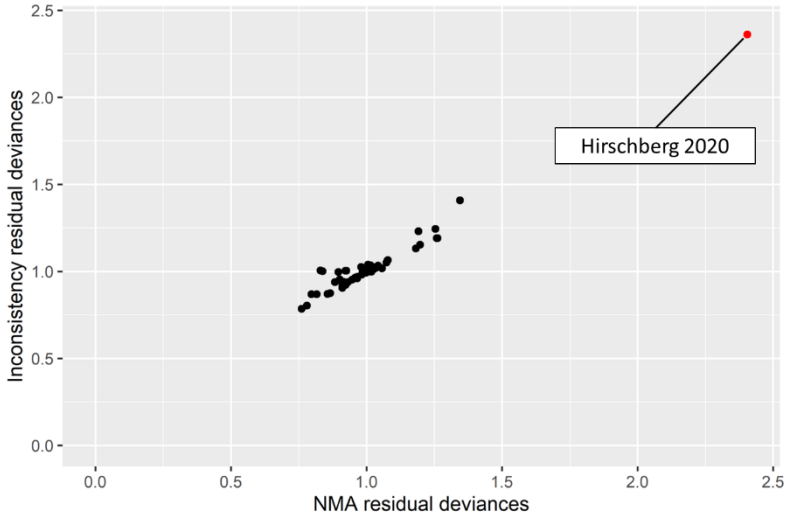


Figure 23: Dev-dev plot. Dryness.



The classes for which there is clear evidence suggesting decreased dryness compared to Inactive treatment (Placebo) are the following (Figure 24):

- DHEA
- Laser
- Laser + vaginal estrogen
- SERM
- Oestradiol
- Conjugated estrogen

Estriol and Progestin + vaginal oestrogen also showed some evidence of decreased dryness compared to Placebo.

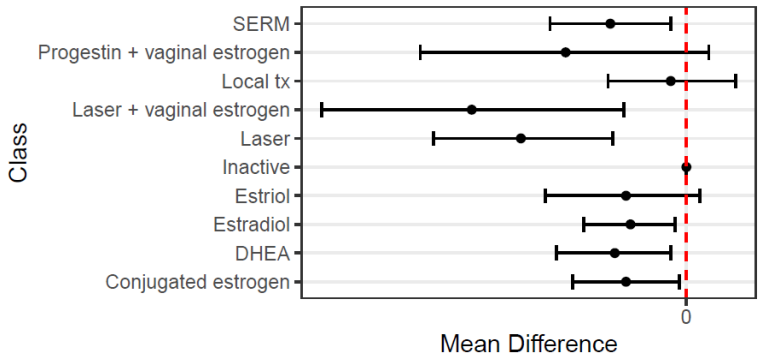
There is evidence of decreased dryness (lower MD corresponds to improved outcomes) compared to Placebo for the following interventions (Figure 24):

- Prasterone
- CO2 laser
- CO2 laser + Estriol cream
- Ospemifene
- Oestradiol tablet
- Oestradiol gel
- Oestradiol cream
- Oestradiol softgel capsule
- Conjugated estrogen tablet
- Conjugated estrogen cream

Whilst there was more uncertainty than for other interventions, there was also some evidence of decreased dryness compared to Placebo for:

- Levonorgestrel Oestradiol tablet
- Estriol cream
- Estriol pessary (0.5mg)
- Estriol gel

Figure 24: Class level dryness. Mean Differences (MD) and 95% credible intervals for every class compared to Inactive (reported on 4-point 0-3 dryness scale). MD < 0 imply a reduction in dryness compared to Inactive.



Mean Difference	95%CrI
−0.34	(−0.61, −0.07)
−0.54	(−1.19, 0.1)
−0.07	(−0.35, 0.22)
−0.96	(−1.63, −0.28)
−0.74	(−1.13, −0.33)
0.00	Reference
−0.27	(−0.63, 0.06)
−0.25	(−0.46, −0.05)
−0.32	(−0.58, −0.07)
−0.27	(−0.51, −0.03)

Laser + vaginal estrogen and Laser are the highest ranked classes with posterior median ranks of 1st (95% CrI 1st to 5th) and 2nd (95% CrI 1st to 5th) respectively (Supplement 14, *"Ranks"* worksheet). However, these classes were investigated on small numbers of patients (15 and 88 respectively in total), which limits the ability to draw strong conclusions on them.

The lowest ranked class is Inactive (placebo) at 10th (95% CrI 8th to 10th), and the lowest ranked active class is Local treatment (9th, 95% CrI 6th to 10th) (Table 384).

Table 38. Posterior median rank and 95% credible intervals by class. Dryness.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Laser + vaginal estrogen	1.59	1 (1, 5)
Laser	2.22	2 (1, 5)
Progestin + vaginal estrogen	3.81	3 (1, 10)
SERM	5.15	5 (2, 9)
DHEA	5.39	5 (2, 9)
Estriol	6.04	6 (3, 9)
Conjugated estrogen	6.06	6 (3, 9)
Estradiol	6.42	7 (4, 9)
Local tx	8.78	9 (6, 10)
Inactive	9.54	10 (8, 10)

Outcome: Vulvovaginal discomfort/irritation (Discomfort)

13 trials were included, comparing 13 interventions and 9 classes (Table 39, Figure 25, Figure 26).

The following internal reference standard deviations[14] were estimated for the following scales, and these were used for standardization when estimating SMDs:

- 4-point scale (0-3): 0.768
- VAS scale (0-10): 2.770
- 5-point scale (0-4): 0.601

A fixed class effects model was selected based on DIC (Table 3 in Supplement 6). There was no evidence of inconsistency (Figure 27). Between-study heterogeneity was slightly lower in the bias-adjusted model compared to the NMA model, yet DIC was similar (Table 3

in Supplement 6) and the estimated bias parameter was highly uncertain (-14.4; 95%CrI: -34.1 to 5.65). Based on this uncertainty and the similarity in DIC we concluded that the base-case model was more appropriate for decision-making, but we highlighted the potential impact of small study effects to the committee. Further details are given in the sensitivity analyses section of this appendix. Reported results are therefore based on the random-effects fixed class NMA model assuming consistency and can be found in Supplement 12.

Low between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau = 0.25$ (95% CrI 0.06, 0.57)). Relative effects are presented compared to Placebo.

Table 39. Table of interventions, classes and number of patients (N) included in Discomfort analysis.

	Intervention	N	Class	N
1	Plc	1280	Inactive	1280
2	Prasterone	150	DHEA	150
3	Co2 laser	88	Laser	88
4	Co2 laser + estriol cream	15	Laser + vaginal estrogen	15
5	Moisturiser	40	Local tx	100
6	Lubricant	60		
7	Ospemifene	313	SERM	313
8	Estriol cream	15	Estriol	65
9	Estriol gel	50		
10	Estradiol tab	258	Estradiol	733
11	Estradiol cream	287		
12	Estradiol gelcap	188		
13	Conj estrogen cream	316	Conjugated estrogen	316

Figure 25: Network diagram of all studies included in analysis by intervention. Discomfort.

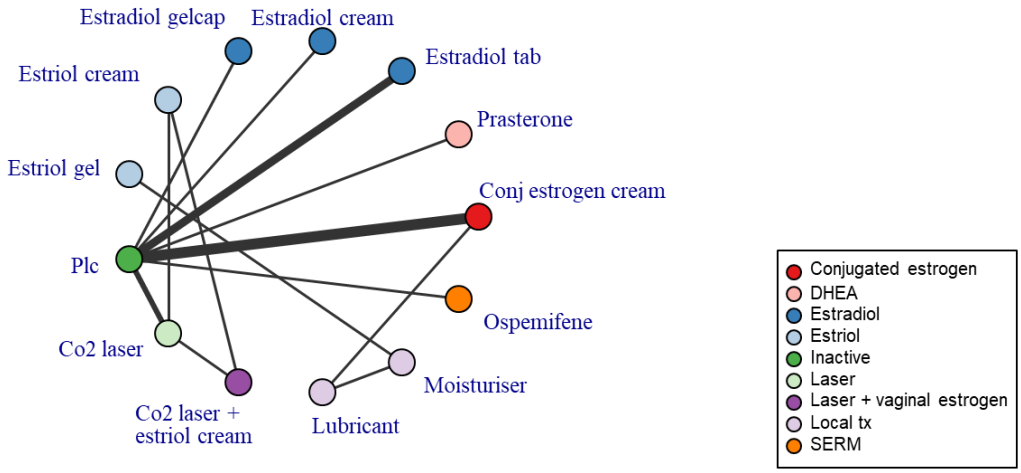


Figure 26: Network diagram of all studies included in analysis by class. Discomfort.

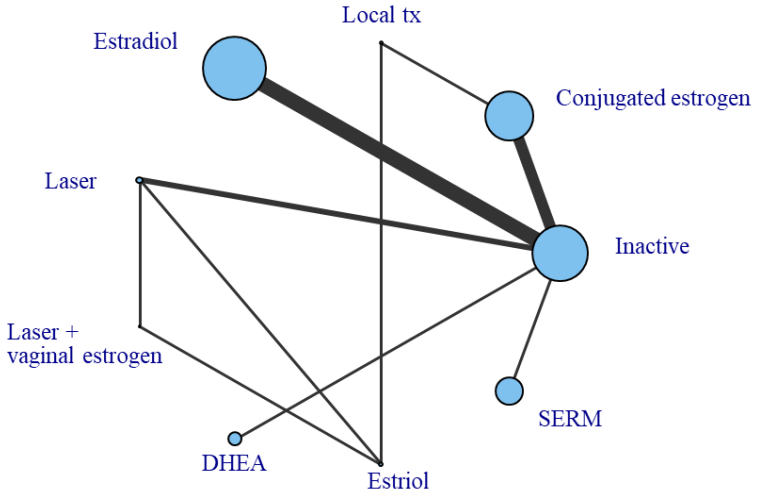
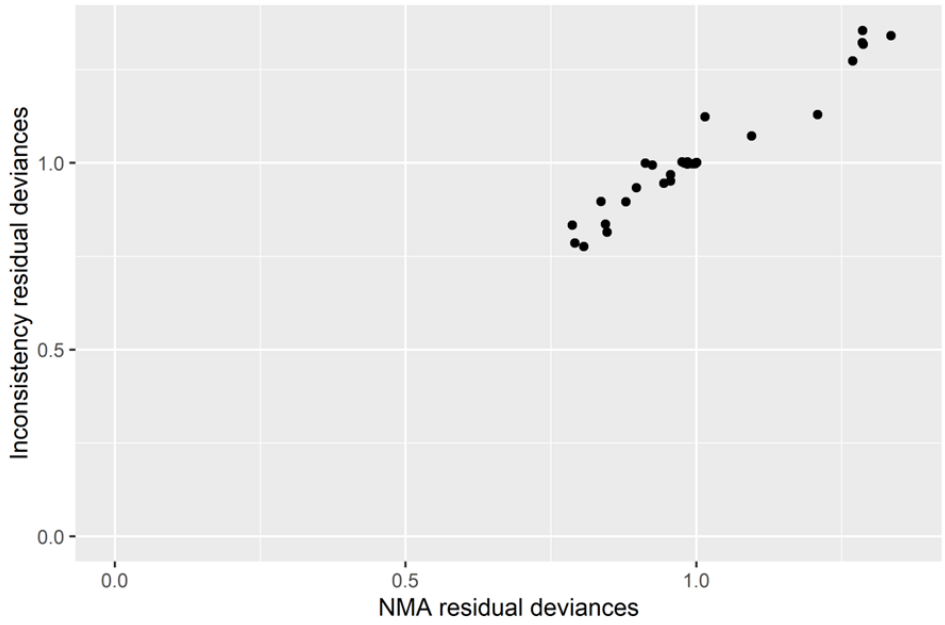


Figure 27: Dev-dev plot. Discomfort.



The classes for which there is clear evidence suggesting decreased discomfort compared to Inactive treatment (Placebo) are the following (Figure 28):

- Laser
- Oestradiol

For Laser + vaginal estrogen the magnitude of credible effects was substantial, but there was considerable uncertainty.

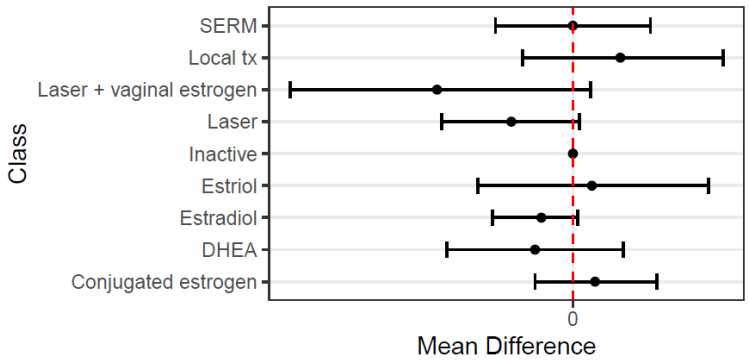
Effects of treatment on discomfort was generally slightly less clear than for dyspareunia and dryness. There was evidence of decreased discomfort (lower MD corresponds to improved outcomes) compared to Placebo for the following interventions (Figure 28):

- CO2 laser
- Oestradiol tablet
- Oestradiol cream

- Oestradiol softgel capsule

For CO2 laser + Estriol cream the magnitude of credible effects was substantial, but there was considerable uncertainty.

Figure 28: Class level discomfort. Mean Differences (MD) and 95% credible intervals for every class compared to Inactive (reported on 4-point 0-3 discomfort scale). MD < 0 imply a reduction in discomfort compared to Inactive.



Mean Difference	95%CrI
0.00	(−0.49, 0.49)
0.30	(−0.32, 0.95)
−0.86	(−1.79, 0.11)
−0.39	(−0.83, 0.04)
0.00	Reference
0.12	(−0.6, 0.86)
−0.20	(−0.51, 0.03)
−0.24	(−0.8, 0.32)
0.14	(−0.24, 0.53)

Laser + vaginal estrogen and Laser are the highest ranked classes with posterior median ranks of 1st (95% CrI 1st to 6th) and 2nd (95% CrI 1st to 6th) respectively (Supplement 12, *"Ranks"* worksheet). However, these classes were investigated on small numbers of patients (15 and 88 respectively in total). This limits the ability to draw strong conclusions on them, as can be seen by the width of credible intervals for mean differences compared to Inactive (placebo).

The lowest ranked class is Local treatment at 8th (95% CrI 4th to 9th).

Table 40. Posterior median rank and 95% credible intervals by class. Discomfort.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Laser + vaginal estrogen	1.52	1 (1, 6)
Laser	2.64	2 (1, 6)
Estradiol	3.75	4 (1, 7)
DHEA	3.82	3 (1, 9)
SERM	5.82	6 (2, 9)
Inactive	5.96	6 (4, 8)
Estriol	6.56	7 (2, 9)
Conjugated estrogen	7.04	7 (4, 9)
Local tx	7.87	8 (4, 9)

Outcome: Pain/discomfort when urinating (Dysuria)

3 trials were included, all of which reported CFB. The studies compared 4 interventions and 4 classes (Table 41, Figure 29, Figure 27). The network was disconnected at both the treatment and class level, and therefore only pairwise comparisons could be made. Sample sizes in the included studies were small, and therefore there is considerable uncertainty in the results.

Poordast 2021 reported a mean difference of 0.010 (95%CI: -0.395, 0.405) for Lubricant versus Conjugated estrogen cream, reported on a 4-point 0-3 discomfort scale (higher

scores correspond to worse symptoms). This suggested no evidence for a difference between the two treatments.

A fixed effects pairwise meta-analysis using SMDs was performed to synthesise two studies (Li 2021 and Salvatore 2021) comparing CO2 laser versus Placebo. Transformed to a 0-10 Visual Analog Scale (higher scores correspond to worse symptoms) the pooled mean difference was -0.681 (95%CI: -1.382, 0.019), suggesting some evidence for a reduction in dysuria symptoms for CO2 laser compared to Placebo.

Table 41. Table of interventions, classes and number of patients (N) included in Dysuria analysis.

	Intervention	N	Class	N
1	Plc	72	Inactive	72
2	Co2 laser	73	Laser	73
3	Lubricant	33	Local tx	33
4	Conj estrogen cream	33	Conjugated estrogen	33

Figure 29: Network diagram of all studies included in analysis by intervention. Dysuria.

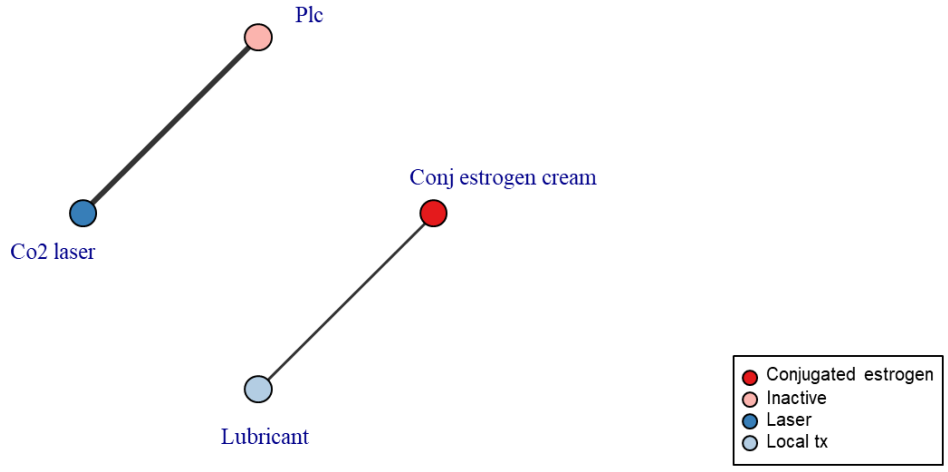
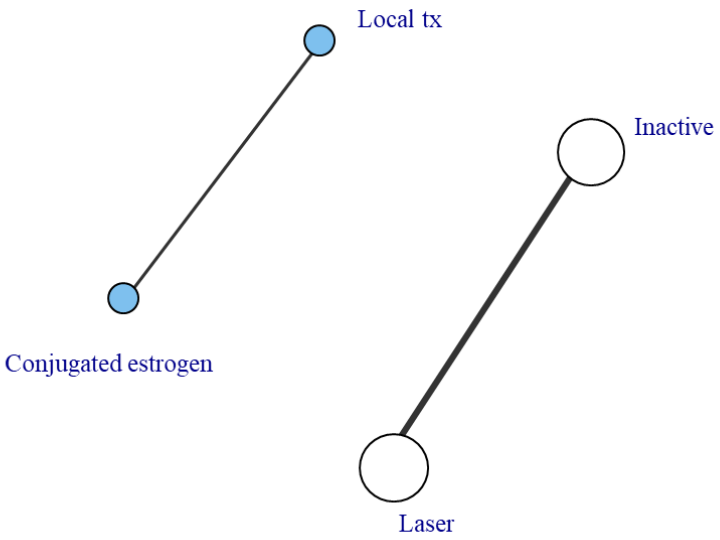


Figure 30: Network diagram of all studies included in analysis by class. Dysuria.



Outcome: Discontinuation due to adverse events (up to 14 weeks follow-up)

Exploratory analyses investigated fitting models using a binomial likelihood with a cloglog link function to account for different study follow-up times[1] (see 'likelihood and link functions' in the methodology section of this appendix). However, this model failed to converge and therefore the reported analyses were conducted using a logit link function. Analyses were restricted to studies reporting numbers of patients who discontinued due to adverse events at up to 14 weeks follow-up to limit the impact of effect modification due to study follow-up. This led to the exclusion of 4 studies (Goldstein 2014, Dessole 2004, Simon 2008, Rioux 2000) that reported outcomes at 16-52 weeks follow-up.

After excluding 13 trials with zero events in all arms, 31 trials of 16 interventions and 8 classes were included for this outcome (Table 42, Figure 31, Figure 32). A continuity correction was applied to data in 9 studies containing at least one zero cell to stabilize the results.

A fixed class effects model was selected based on DIC (Table 4 in Supplement 6).

Between-study heterogeneity was similar in the NMA and inconsistency models, with slightly higher DIC in the inconsistency model than the NMA model, suggesting no evidence of global inconsistency. The prediction of individual studies was similar in both models, though two studies (Lima 2013 and Bachmann 1997) had high deviance values (Figure 33), caused by arms with zero responders to which a continuity correction had been added.

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted, though no evidence of bias was identified (Table 4 in Supplement 6). Further details are given in the sensitivity analyses section of this appendix.

Reported results are based on the fixed class random treatment effects NMA model, assuming consistency and can be found in Supplement 10. Low between trial heterogeneity was observed relative to the size of the intervention effect estimates

$(\tau = 0.22\ (95\%\ \text{CrI}\ 0.01\ \text{to}\ 0.70))$. Relative effects are presented as Odds Ratios (OR) compared to Placebo.

Table 42. Table of interventions, classes and number of patients (N) included in Discontinuation analysis.

	Intervention	N	Class	N
1	Plc	2685	Inactive	2685
2	Prasterone	711	DHEA	711
3	Co2 laser	45	Laser	45
4	Moisturiser	120	Local tx	247
5	Lubricant	127		
6	Ospemifene	1052	SERM	1052
7	Estriol cream	239	Estriol	747
8	Estriol pess	289		
9	Estriol pess 50	53		
10	Estriol gel	166		
11	Estradiol tab	344	Estradiol	1424
12	Estradiol ring	581		
13	Estradiol cream	287		
14	Estradiol gelcap	212		
15	Conj estrogen tab	35	Conjugated estrogen	592
16	Conj estrogen cream	557		

Figure 31: Network diagram of all studies included in analysis by intervention. Discontinuation.

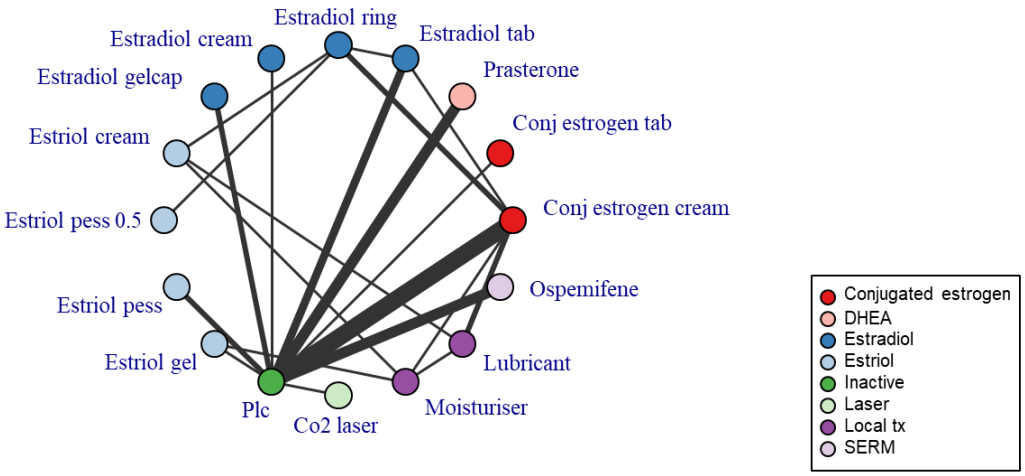


Figure 32: Network diagram of all studies included in analysis by class. Discontinuation.

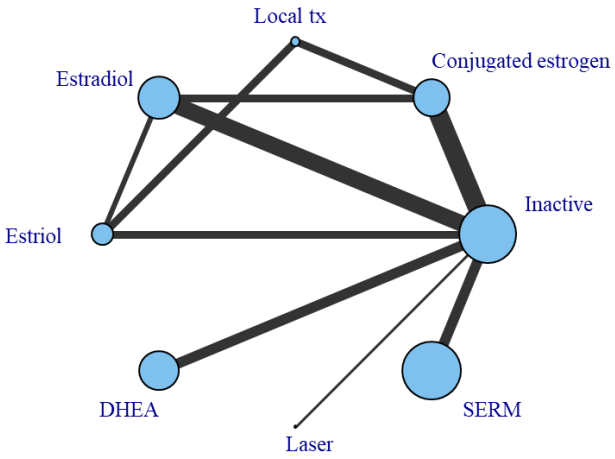
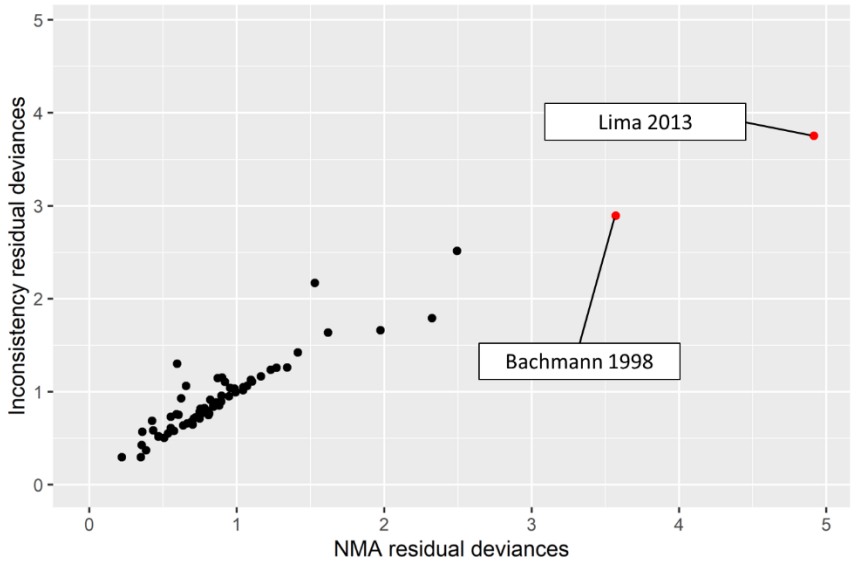


Figure 33: Dev-dev plot. Discontinuation.



The only class for which there is clear evidence suggesting a lower odds of discontinuation compared to Placebo is Local treatment (Figure 34). However, there was weaker, less clear evidence for an increased odds of discontinuation compared to Placebo for:

- Oestradiol
- Conjugated estrogen

There is evidence of a decreased odds of discontinuation (lower OR corresponds to lower discontinuation) compared to Placebo for the following interventions (Figure 34):

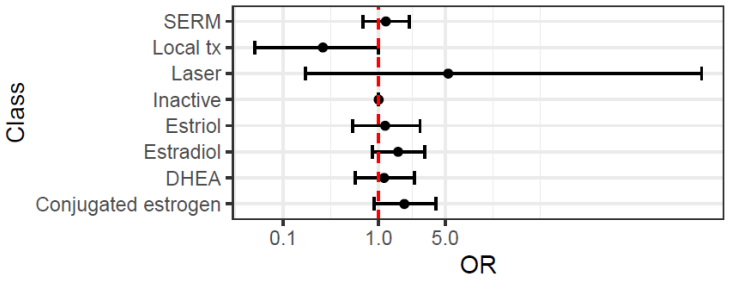
- Moisturiser
- Lubricant

There was also weaker, less clear evidence for an increased odds of discontinuation compared to Placebo for:

- Oestradiol tablet
- Oestradiol ring

- Oestradiol softgel capsule
- Oestradiol cream
- Conjugated estrogen tablet
- Conjugated estrogen cream

Figure 34: Class level discontinuation due to adverse events. Odds Ratios (OR) and 95% credible intervals for every class compared to Inactive for discontinuation due to adverse events. OR > 1 imply a reduction in discontinuation due to adverse events compared to Inactive.



OR	95%CrI
1.19	(0.68, 2.08)
0.26	(0.05, 1)
5.37	(0.17, 2440.6)
1.00	Reference
1.17	(0.53, 2.72)
1.60	(0.86, 3.03)
1.14	(0.57, 2.36)
1.86	(0.89, 4.01)

Local treatment is the highest ranked class with a posterior median rank of 1st (95% CrI 1st to 3rd), followed by Inactive (Placebo) with a posterior median rank of 3rd (95% CrI 2nd to 5th). The lowest ranked classes are Laser and Conjugated estrogen, with posterior median ranks of 8th (95% CrI 1st to 8th) and 7th (95% CrI 3rd to 8th) respectively (Supplement 10, *"Ranks"* worksheet).

Table 43. Posterior mean and median rank and 95% credible intervals by class. Discontinuation.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Local tx	1.15	1 (1, 3)
Inactive	3.24	3 (2, 5)
DHEA	4.19	4 (2, 8)
Estriol	4.29	4 (2, 8)
SERM	4.36	4 (2, 7)
Estradiol	5.82	6 (3, 8)
Conjugated estrogen	6.38	7 (3, 8)
Laser	6.58	8 (1, 8)

Sensitivity analyses

Prespecified sensitivity analyses

Pain during/after sex (Dyspareunia)

Results were similar between base-case and bias-adjusted NMA models, with only very minimal changes in relative effects compared to Inactive (Placebo) for most interventions. (Figure 1 in Supplement 7). Model fit statistics indicated there was no clear evidence of bias due to small-study effects (Table 1 in Supplement 6).

Base-case analyses included studies with the latest available follow-up up to 52 weeks. Analysis of only studies with up to 12 weeks follow-up was also explored to investigate the impact of study follow-up on treatment effects (Figure 2 in Supplement 7). Mean differences versus Inactive (Placebo) were very similar to the base-case analysis for all classes apart from Laser, in which the effect was lower when longer follow-up studies were included. Laser + vaginal estrogen was only explored in a study reporting results at 20 weeks, so results were not available for analyses at 2-12 weeks follow-up.

Vulvovaginal dryness (Dryness)

Results were similar between base-case and bias-adjusted NMA models, with only very minimal changes in relative effects compared to Inactive (Placebo) for most interventions. (Figure 3 in Supplement 7). Model fit statistics indicated there was no evidence of bias due to small-study effects (Table 2 in Supplement 6).

Base-case analyses included studies with the latest available follow-up up to 52 weeks. Analysis of only studies with up to 12 weeks follow-up was also explored to investigate the impact of study follow-up on treatment effects (Figure 4 in Supplement 7). Mean differences versus Inactive (Placebo) were very similar to the base-case analysis. Laser + vaginal estrogen was only explored in a study reporting results at 20 weeks, so results were not available for analyses at 2-12 weeks follow-up.

Vulvovaginal discomfort/irritation (Discomfort)

There were some differences in results between base-case and bias-adjusted NMA models, with reductions in efficacy versus Inactive (Placebo) notably lower for Laser and Laser + vaginal estrogen (Figure 5 in Supplement 7). 95%CrIs for relative effects were wider in the bias-adjusted model, with effects slightly pulled towards zero due to the assumption that bias favoured active versus inactive treatments. Model fit statistics suggested there was no clear evidence of bias due to small-study effects (Table 3 in Supplement 6), but due to slightly lower between-study heterogeneity and minor differences in treatment effects in the bias-adjusted model compared to the NMA model we highlighted the potential impact of small study effects to the Committee.

Base-case analyses included studies with the latest available follow-up up to 52 weeks. Analysis of only studies with up to 12 weeks follow-up was also explored to investigate the impact of study follow-up on treatment effects (Figure 6 in Supplement 7). Mean differences versus Inactive (Placebo) were typically higher in shorter-term studies than in the base-case analysis (2-52 weeks follow-up) for Conjugated Estrogen, Estriol, SERM and Local treatment, suggesting that these classes may be less effective at longer follow-up. Laser and

Laser + vaginal estrogen were only explored in studies reporting longer-term follow-up, so results were not available for analyses at 2-12 weeks follow-up.

Discontinuation due to adverse events

Results were similar between base-case and bias-adjusted NMA models, with only very minimal changes in relative effects compared to Inactive (Placebo) for most interventions. (Figure 7 in Supplement 7). Model fit statistics indicated there was no evidence of bias due to small-study effects (Table 4 in Supplement 6).

Post hoc sensitivity analyses

In addition to the pre-specified sensitivity analysis several post-hoc sensitivity analyses were performed to explore aspects of the data and modelling process that may have strongly impacted results.

For Dyspareunia and Dryness outcomes we investigated the impact of combining studies reporting ITT results with those that only reported results in patients who completed treatment and had <10% dropout.

For Dyspareunia, Conjugated estrogen, Estriol, Local treatment, Laser + vaginal estrogen and Laser showed slightly greater efficacy versus Inactive (Placebo) in analysis of only studies reporting ITT, though results were considerably more uncertain and base-case NMA results were mostly within 95% credible intervals of ITT only results (Figure 8 in Supplement 7). This may indicate that even at quite low rates of dropout attrition bias may be present, but as this leads to the exclusion of 10 studies (24 in base-case and 14 in ITT only) results are highly uncertain and therefore present challenges for decision-making.

For Dryness treatment effects versus Inactive (Placebo) are very similar from the base-case and ITT only analyses, though with less uncertainty in the base-case analysis that includes studies reporting results in patients who completed treatment and had <10% dropout, due to the inclusion of 9 additional studies (Figure 9 in Supplement 7).

This could not be explored for Discomfort as the exclusion of only studies that reported ITT led to the network being disconnected at the class level and thus mean differences between all treatments/classes of interest could not be estimated.

We explored the impact of excluding Mitchell 2018 on inconsistency in the analysis of Dyspareunia. Exclusion of this study from the network resolved the inconsistency and improved model fit, though we have included it in base-case analyses based on both the Committee's preference and because there were no concerns regarding the conduct of the trial.

Sensitivity of recommendations to NMA results

In the original protocol (see Appendix A) we had intended to perform threshold analysis[16] to explore how much the NMA evidence would need to change for the recommendations made by the Committee to change. Of the treatments that were explored in sufficiently large numbers of patients, efficacies were very similar, with no clear "best" treatment, and we therefore did not believe that threshold analysis solely around an optimal treatment based on the NMA results would be useful for decision making.

Given the importance of cost effectiveness in informing these recommendations, and more widely within NICE, changes in the effectiveness evidence for the interventions of most

interest in the NMA were explored during sensitivity analysis in the bespoke economic model based on the NMA results.

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