South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: Gynaecology

EVIDENCE SUMMARY

Date: 22 July 2021

Reviewer: Prof GS Gebhardt

Affiliation and declaration of interests: GSG (Department of Obstetrics and Gynaecology, Stellenbosch University, PHC/Adult Hospital Level Committee member) has no interests to declare with respect to transdermal hormone patches.

RESEARCH QUESTION: Are Transdermal Patches an effective, acceptable and safe alternative route for hormone replacement therapy in women with vasomotor symptoms of menopause?

Eligibility criteria for inclusion of studies:
Population: Postmenopausal women with vasomotor symptoms

Intervention: Treatment with oral estrogen

Comparison: Treatment with transdermal estrogen

Outcome: Efficacy (relief of symptoms); safety and acceptability

Study designs: Systematic reviews of RCTs

BACKGROUND

Hormone replacement therapy (HT) for short-term symptomatic relief of severe menopausal symptoms are currently available in the STG as oral preparations only (estradiol valerate or conjugated oestrogens in various strengths) with or without progesterone. Women without a uterus (e.g. post-hysterectomy) use estrogen only, while women with an intact uterus needs additional progesterone for endometrial protection. This is given either as sequentially opposed or continuous combined regimens. Estrogen is available in many other forms, including transdermal patches, gels, emulsions and lotions, intravaginal creams and tablets, vaginal rings and subcutaneous implants, but currently only oral preparations are available on the EDL. There is a supply challenge with conjugated estrogen and the PHC/Adult Hospital Committee is exploring alternative formulations/routes for administration of HT.

Transdermal HT patches

The table below lists the transdermal HT options currently available on the South African market.

TRANSDERMAL HT PREPARATIONS - SEP					
Trade Name	**Contents**	**Usage**	**Tender price (28d) (ZAR)**	**SEP (28d) (ZAR)**	**60% of SEP (28d) (ZAR)**
Estradot 25 mcg®	Oestradiol hemihyd-25mcg	Estrogen only (unopposed)	-	180.21	108,13
Estradot 37.5 mcg®	Oestradiol hemihyd-37 5mcg	Estrogen only (unopposed)	-	180.21	108,13
Estradot 50 mcg®	Oestradiol hemihyd-50mcg	Estrogen only (unopposed)	-	207.21	124,32
Estradot 75 mcg®	Oestradiol hemihyd-75mcg	Estrogen only (unopposed)	-	207.21	124,32
Estradot 100 mcg®	Oestradiol hemihyd-100mcg	Estrogen only (unopposed)	-	207.21	124,32
Evorel 25 tts®	Oestradiol-1 6mg	Estrogen only (unopposed)	-	194.07	116,44
Evorel 50 tts®	Oestradiol-3 2mg	Estrogen only (unopposed)	-	209.71	125,82
Evorel 75 tts	Oestradiol-4 8mg	Estrogen only (unopposed)	-	218.87	131,32
Evorel 100 tts®	Oestradiol-6 4mg	Estrogen only (unopposed)	-	228.64	137,19
Climara 50®	Oestradiol-3 9mg	Estrogen only (unopposed)	-	180.13	108,08
Estalis 50/140®	Norethis acet-2 7mg; Oestradiol hemihyd-0 62mg	Continuous combined (estrogen with progesterone)	-	289.27	173.56
Evorel conti®	Oestradiol-3 2mg; Norethis acet-11 2mg;	Continuous combined (estrogen with progesterone)	-	345.36	207.21
Evorel sequi®	Oestradiol-3 2mg; Oestradiol-3 2mg; Norethis acet-11 2mg	Sequential use (estrogen with progesterone)	-	366.60	201.96

ORAL HT PREPARATIONS CURRENTLY ON TENDER					
Trade Name	**Contents**	**Usage**	**Tender price (28d) (ZAR)**	**SEP (28d) (ZAR)**	**60% of SEP (28d) (ZAR)**
Estrofem 1 mg®	Estradiol 1 mg	Estrogen only (unopposed)	40.31	154.97	92.98
Estrofem 2 mg®	Estradiol 2 mg	Estrogen only (unopposed)	75.78	168.92	101.35
Premarin 0.3 mg®	Conjugated oestrogens-0 3mg	Estrogen only (unopposed)	123.02	133.85	80.31
Activelle®	Estradiol-1mg Norethis acet-0 5mg	Continuous combined (estrogen with progesterone)	94.43	239.21	143.53
Kliogest®	Estradiol-2mg Norethis acet-1mg	Continuous combined (estrogen with progesterone)	109.53	308.02	184.51

METHODS:
Five data sources were searched: Pubmed, Cochrane Library, Epistemonikos, NICE Guidelines and Google scholar.

i. Pubmed

Search strategy
((("administration, cutaneous"[MeSH Terms] OR ("administration"[All Fields] AND "cutaneous"[All Fields]) OR "cutaneous administration"[All Fields] OR "transdermal"[All Fields] OR "transdermally"[All Fields] OR "transdermals"[All Fields] OR "transdermic"[All Fields] OR "transdermically"[All Fields]) AND ("estrogen s"[All Fields] OR "estrogene"[All Fields] OR "estrogenes"[All Fields] OR "estrogenic"[All Fields] OR "estrogenically"[All Fields] OR "estrogenicities"[All Fields] OR "estrogenicity"[All Fields] OR "estrogenization"[All Fields] OR "estrogenized"[All Fields] OR "oestrogen"[All Fields] OR "estrogens"[Pharmacological Action] OR "estrogens"[MeSH Terms] OR "estrogens"[All Fields] OR "estrogen"[All Fields] OR "oestrogen s"[All Fields] OR "oestrogenic"[All Fields] OR "oestrogenically"[All Fields] OR "oestrogenicity"[All Fields] OR "oestrogenization"[All Fields] OR "oestrogens"[All Fields]) AND ("vasomotor"[All Fields] OR "vasomotoric"[All Fields] OR "vasomotoricity"[All Fields] OR "vasomotors"[All Fields])) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])

10 systematic reviews was retrieved, of which four (Corbelli et al(1) and Derzko et al(2) and Nelson et al(3) and Mohammed et al(4) was relevant to the PICO and two more (the NICE(5) guideline and the Marjoribanks(6) Cochrane review) was already retrieved (see below). 58 randomised control trials were retrieved, of which only one (Akhila et al) was recent and relevant to the PICO and not included in one of the systematic reviews.(7)

ii. Cochrane Library

Search strategy:
"transdermal" in Title Abstract Keyword AND “vasomotor” OR “menopausal” in Title Abstract Keyword - in Cochrane Reviews, Cochrane Protocols (Word variations have been searched)

76 Cochrane reviews and 6 Cochrane protocols were retrieved; of which 2 Cochrane reviews (Marjoribanks(6) et al, 2017) and Boardman(8) et al (2015) were reviewed (but see below) as other literature was not relevant to the PICO question.

iii. Epistemonikos

Search strategy:
(title:(TRANSDERMAL AND VASOMOTOR OR MENOPAUSAL) OR abstract:(TRANSDERMAL AND VASOMOTOR OR MENOPAUSAL))

15 primary studies and 17 systematic reviews were retrieved, but (apart from the two Cochrane reviews already mentioned) none of the systematic reviews were relevant to the PICO question and the primary studies were those already identified via PubMed, conducted in the 1990s. Two more recent primary studies were excluded as not relevant to the PICO (comparison was with placebo). A systematic review by Abdi(9) et al (Hormone Therapy for Relieving Postmenopausal Vasomotor Symptoms; 2015) were excluded as the comparator was placebo and the intervention any form of hormone therapy (oral, gels, spray and transdermal).

iv NICE guidelines

One NICE guideline (Menopause: diagnosis and management) contained information that was relevant to the PICO. One systematic review (Sweetland(10) et al) was identified from a reference search.

v: Google Scholar: The review by Grant(11) was found by a Google scholar search.

RESULTS

Description of studies

Transdermal HT is in general use for the last 30 years and the randomised trials and acceptability studies were mostly done in in the early 1990s (e.g. Pornell et al(12) and Gordon(13)). There were no recent (since 2010) randomised trials or systematic reviews comparing the transdermal route with the oral route.

The Nelson et al systematic review from 2004(3) included 32 trials with 14 trials meeting criteria for meta-analysis. All estrogen agents regardless of route significantly reduced the weekly number of hot flashes compared with placebo (conjugated estrogen, 1 trial: mean change, –19.1; 95% confidence interval [CI], –33.0 to –5.1; oral 17ß-estradiol, 5 trials: pooled weighted mean difference, –16.8; 95% CI, –23.4 to –10.2; transdermal 17-estradiol, 6 trials: pooled weighted mean difference, –22.4; 95% CI, –35.9 to –10.4). There was no significant differences between agents.

The Corbelli(1) systematic review was excluded as the comparator was placebo and the Derzko(2) review was excluded as the comparison was with estrogen gel and placebo.

The NICE guideline(5) on the diagnosis and treatment of menopause use the blanket term HT (hormone replacement therapy) and does not make individual recommendations for different routes of administration except in the case of women at higher risk for venous thromboembolism(VT) (including a BMI>30kg/m^2), where the transdermal route is recommended. The evidence for this is summarised in appendix H(14) of the NICE guideline and is based largely on the 2012 study by Sweetland et al(10) where more than 1 000 000 women on HT were assessed for risk for thromboembolism (for effectively more than 3 million person years of follow-up). The VT risk was significantly greater for oral estrogen-progestin than oral estrogen-only therapy (RR = 2.07 [95%CI, 1.86 to 2.31] vs. 1.42 [1.21 to 1.66]), with no increased risk with transdermal estrogen-only therapy (0.82 [0.64 to 1.06]). Current use of transdermal oestrogen only HT in women aged 50+ years had a RR for VT of 0.85 (95% CI 0.61 to 1.20), while current use of oral oestrogen only HT in women aged 50+ years had a RR of 1.33 (1.06 to 1.65) .

A systematic review and meta-analysis by Mohammed et al on oral vs transdermal estrogen therapy and vascular events included the Sweetland study with 14 more observational studies at moderate risk of bias.(4) When compared to transdermal estrogen, oral estrogen was associated with increased risk of a first episode of VT (RR, 1.63; 95% CI, 1.40 to 1.90; I^2 = 53%), deep vein thrombosis (RR, 2.09; 95% CI, 1.35 to 3.23; I^2 = 0 %), and possibly stroke (RR, 1.24; 95%CI, 1.03 to 1.48; a single case-controlled study). The meta-analysis appears below – see figure 1.

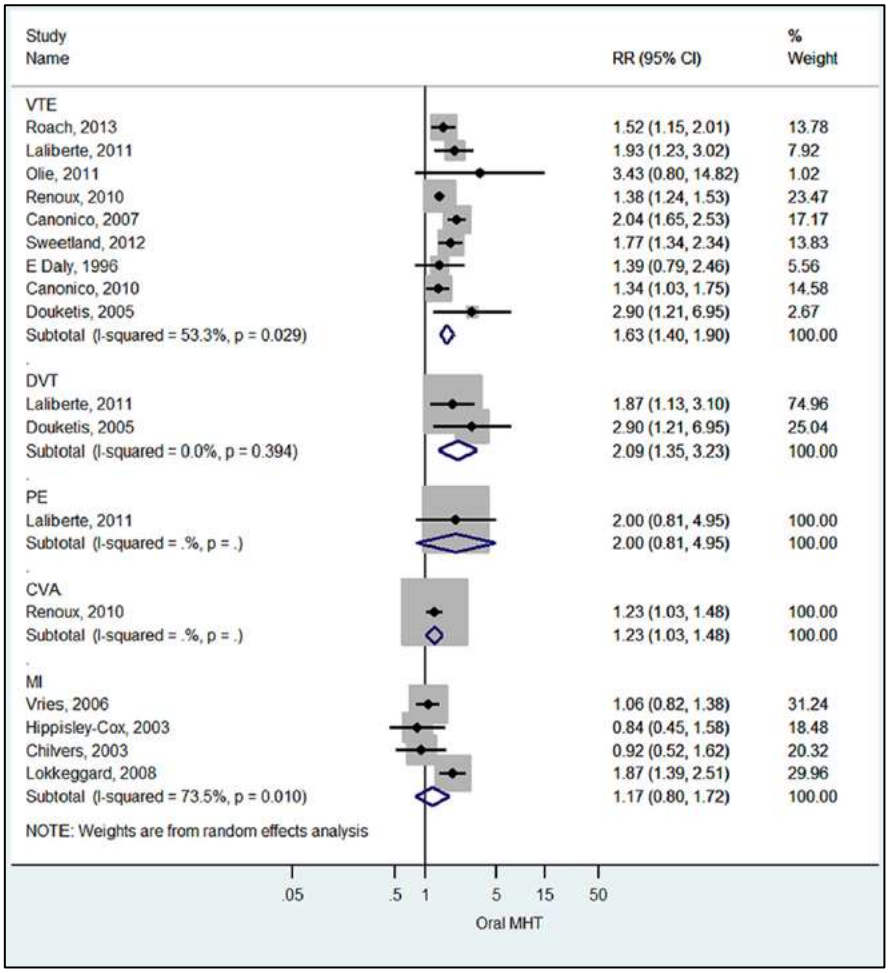

Figure 1: Forest plot comparing oral vs other HT therapies, assessing associated vascular adverse effects.

Grant et al prepared a comprehensive analysis of the comparative effectiveness of therapies for menopausal symptoms for the Agency for Healthcare Research and Quality by Grant and co-workers (11) of 238 trials, concluded that there is considerable certainty that estrogens are the most effective treatment for relieving vasomotor symptoms and are accompanied by the greatest improvement in quality-of-life measures. They again used any available route of estrogen (high dose or low dose) as a comparator and did not compare various estrogen routes with each other.

The two Cochrane reviews identified did not address the PICO directly- the Marjoribanks(6) review looked at safety (mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition) with any type of hormonal preparation. The one metanalysis of patch data and risk of possible venous thromboembolism (Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome Venous thromboembolism (DVT or PE): oestrogen-only HT did not show a significant increased risk in any of the studies included (for patch the relative risk versus placebo was 0,4 with 95% CI 0.02-9.73).

The Boardman(8) Cochrane review was excluded as it only investigated oral preparations and the risk for cardiovascular with no comparison to patches.

SUMMARY

- Estrogen, regardless of route, is an effective method for relief of vasomotor menopausal symptoms.
- Only the oral route is currently available to women on the EML, and there are supply constraints.
- The transdermal route (patch) is as effective, it is acceptable and probably safer (less risk for thrombotic events in observational studies).

RECOMMENDATION

Based on this evidence summary, the PHC/Adult Hospital Level Committee proposes that transdermal estrogen patches be considered for inclusion on the EML for the management of vasomotor symptoms in menopause. Because of its higher cost, use may be restricted to women with previous history of thrombotic events.

Rationale: Available evidence shows that all estrogen agents regardless of route of administration significantly reduces vasomotor symptoms of menopause with improved quality-of-life measures, compared with placebo. When compared to transdermal estrogen, oral estrogen was associated with increased risk of a first episode of VT, deep vein thrombosis and possibly stroke.

Level of evidence: Moderate certainty evidence

Review indicator: Price (expand indication to all if price is reasonable)

NEMLC MEETING OF 19 DECEMBER 2021

Discussion: The risk for first time thrombosis was reported to be higher amongst women on oral HT compared to those using transdermal HT. However, the number of women needing HT who have a high risk of thromboembolism was anticipated that this would be a small number[1]. Citalopram is recommended for treatment of menopausal symptoms in women at high risk of thromboembolism at secondary level of care. Furthermore, NEMLC raised concerns regarding the high price of transdermal HT.

Recommendation: NEMLC deliberated on the proposal suggested by the PHC/Adult Hospital Level Commitee and recommended that HT transdermal patches be removed from the STG, but be added to the therapeutic interchange database as an alternative to oral estrogens.

Rationale: The number of women requiring HT at high risk of thromboembolism is anticipated to be small. Transdermal HT is expensive compared to oral HT preparations. Citalopram is included on the secondary level EML for management of perimenopausal or menopausal syndrome where "oral" HT is contra-indicated, poorly tolerated or ineffective.

Level of Evidence: Conditional recommendation, moderate certainty evidence

References:

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[1] Previously, NEMLC had recommended venlafaxine, oral (for hormone with hormone-dependant cancers) not be included on the national EML for secondary level of care; but rather for consideration at tertiary and quaternary level of care – NEMLC minutes of the meeting of 14 December 2017.

9. Abdi F, Mobedi H, Mosaffa N, Dolatian M, Ramezani Tehrani F. Hormone Therapy for Relieving Postmenopausal Vasomotor Symptoms: A Systematic Review. Arch Iran Med. 2016 Feb;19(2):141–6.
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