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## FEMALE SEXUAL FUNCTION

# Surgical Menopause and Bilateral Oophorectomy: Effect of Estrogen-Progesterone and Testosterone Replacement Therapy on Psychological Well-being and Sexual Functioning; A Systematic Literature Review

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## ABSTRACT

**Background:** Besides experiencing vasomotor symptoms, after surgical menopause and bilateral salpingo-oophorectomy (BSO), women experience moderate to severe psychological and sexual symptoms.

**Aims:** To systematically review and meta-analyze the effect of systemic hormone replacement therapy (sHRT) on psychological well-being and sexual functioning in women after surgical menopause and BSO.

**Methods:** Medline/Pubmed, EMBASE and PsychInfo were systematically searched until November 2021. Randomized controlled trials investigating the effect of sHRT on psychological well-being and/or sexual functioning in surgically menopausal women and women after BSO were eligible for inclusion. Two independent authors performed study selection, risk of bias assessment and data extraction. Standardized mean differences (SMDs) were calculated.

**Outcomes:** Primary outcomes for psychological well-being were defined as overall psychological well-being, depression, and anxiety. Primary outcomes for sexual functioning were defined as overall sexual functioning, sexual desire, and sexual satisfaction. All outcomes were assessed on short ( $\leq 12$  weeks) or medium term (13–26 weeks).

**Results:** Twelve studies were included. Estradiol had a beneficial effect on depressed mood on short term 3–6 years after surgery or 2 years (median) after surgery with high heterogeneity (SMD:  $-1.37$ , 95%CI:  $-2.38$  to  $-0.37$ ,  $P = .007$ ,  $I^2$  79%). Testosterone had a beneficial effect on overall sexual functioning on short to medium term 4.6 years (mean) after surgery (SMD 0.38, 95%CI 0.11–0.65,  $I^2$  0%) and on sexual desire on medium term at least 3–12 months after surgery (SMD 0.38, 95%CI 0.19–0.56,  $I^2$  54%). For most studies, risk of bias was uncertain.

**Clinical implications:** Estradiol may beneficially affect psychological symptoms after surgical menopause or BSO and testosterone might improve sexual desire and overall sexual functioning.

**Strengths and limitations:** This review only included patient-reported outcomes, thereby reflected perceived and not simply objective symptoms in surgically menopausal women and women after BSO. The small number of studies highly varied in nature and bias could not be excluded, therefore our results should be interpreted with great caution.

**Conclusion:** Independent randomized controlled clinical trials investigating the effects of estrogen-progesterone and testosterone on psychological and sexual symptoms after surgical menopause are needed.

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**Key Words:** BRCA1/2 mutation; Oophorectomy; Hormone replacement therapy; Psychosexual functioning; Testosterone

## INTRODUCTION

Menopause can cause a variety of vasomotor, psychological, and sexual symptoms.<sup>1–3</sup> After a bilateral salpingo-oophorectomy at premenopausal age, eg, for reducing ovarian cancer risk or for removing benign disease, women experience more severe menopausal symptoms compared to naturally menopausal women.<sup>4,5</sup> The abrupt loss of ovarian hormone synthesis after oophorectomy before menopause calls for considerable psychological and physical adjustment and impacts the quality of life and sexual functioning of these women for many years.<sup>6–8</sup>

To compensate for the loss of ovarian hormones after bilateral salpingo-oophorectomy (BSO), women receive systemic hormone replacement therapy (sHRT), mostly in the form of estrogen and progesterone if the uterus is left in situ, or estrogen-only after hysterectomy.<sup>9</sup> This is especially relevant for women with a *BRCA1/2* mutation who are advised to undergo risk-reducing salpingo-oophorectomy (RRSO) at a relatively young age (35–45 years).<sup>10</sup> sHRT is effective in reducing vasomotor symptoms, but the effect of sHRT on psychological well-being and sexual functioning is still under debate.<sup>11–16</sup> There are several (combinations and forms of) systemic hormonal drugs available to treat menopausal symptoms: estrogen and/or progesterone and/or testosterone, which may explain some of the measured differences in efficacy. Besides, different routes of administration (oral, transdermal, local, or via injection) and dose may also influence the efficacy of HRT to reduce the different menopausal symptoms.<sup>17–21</sup>

The effect of sHRT use on psychological well-being and sexual functioning in women after surgical menopause or BSO has not been systematically reviewed and meta-analyzed up until now.<sup>22</sup> Therefore, the aim of this systematic review is to add a qualitative and quantitative examination on the existing evidence of the effect of sHRT on psychological and sexual functioning in women after surgical menopause and/or BSO.

## METHODS

The protocol for this systematic review and meta-analysis was registered in the PROSPERO database (CRD42019136698). The Preferred Reporting items for Systematic Reviews and

Meta-Analysis (PRISMA) statement was used to report this systematic literature and meta-analysis.<sup>23</sup>

## Search Strategy and Eligibility Criteria

EMBASE, Medline/Pubmed and Psychinfo were used to systematically search for relevant articles published until November 2021. Titles and abstracts were searched for combinations of relevant terms including, but not limited to, surgical menopause, oophorectomy, hormone replacement therapy, sexual functioning, and psychological well-being. The full search strategy is provided in the Appendix (Table A.1). References of selected articles were checked to search for potentially eligible articles, as well as references from existing reviews on similar topics.

Studies eligible for this review included randomized controlled trials (RCTs) and randomized cross-over trials (RCOTs) that evaluated the effect of different forms of estrogen replacement therapy, estrogen-progesterone replacement therapy, tibolone and/or testosterone replacement therapy on sexual functioning and/or psychological well-being as a main outcome in adult women who experienced surgical menopause and/or underwent a BSO. The type of sHRT under investigation had to have a systemic effect, ie, delivered orally, transdermal or via injection. Inclusion was limited to studies that investigated the effect of sHRT on patient-reported symptoms, for the aim of this study was to investigate the effect of sHRT on perceived symptoms. Moreover, studies were only included if published in peer-reviewed journals and if an English full text was available.

Studies were excluded if interventions were only delivered locally and systemic effects were not measured (eg, vaginal creams or other creams) and if there was no comparison to placebo or another control condition. If only physical measures were investigated (eg, lubrication measured with filter papers, blood hormone levels), studies were also excluded. If testosterone was the intervention of interest, use of estrogen as a co-intervention was allowed, but it was not allowed as a control intervention. No publishing year limit was established until November 2021.

Primary outcomes for psychological well-being were defined as overall psychological well-being, depression, and anxiety. Primary outcomes for sexual functioning were defined as overall sexual functioning, sexual desire, and sexual satisfaction. Other

outcomes related to psychological well-being and sexual functioning were extracted, but not used in the analyses.

## Study Selection and Data Extraction

Study selection, risk of bias assessment and data extraction were performed by 2 independent authors (AS, DI or AS, LL) with predefined forms. Before retrieving the full text for detailed evaluation of eligibility, studies were assessed based on title and abstract. Risk of bias assessment was performed with the Cochrane risk of bias tool.<sup>24</sup> In case of disagreement, the goal was to reach consensus between the review authors (AS, DI or AS, LL). If no consensus was reached, 2 other authors were consulted (GB, MM).

Data extracted included population characteristics (sample size, age and reason for menopause), intervention characteristics (type, dose, administration and duration of use), co-interventions and their regimens, outcome measures used (questionnaires, range, direction, results, and time points) and funding sources and their involvement. The data extraction form and the extracted data can be requested by contacting the corresponding author.

## Statistical Analysis

To evaluate the effects of sHRT on the primary outcomes, psychological and sexual symptoms, our aim was to perform a random effects meta-analysis with inverse variance method. Per study, standardized mean differences (SMDs) were calculated with a 95% confidence interval (95% CI), based on mean endpoints or mean changes from baseline and a standard deviation. Results were pooled per type of sHRT (estrogen, estrogen + progesterone, tibolone, testosterone) and per primary outcome. Heterogeneity was assessed with  $I^2$ ,  $\chi^2$  test and  $P$ -value.

Publication bias could not be assessed due to a low number of studies included. For the same reason, subgroup analyses and sensitivity analyses could not be performed. All analyses were performed using Review Manager (RevMan version 5.3.5).

## RESULTS

### Study Selection

After removing duplicates, 2,654 records were screened based on title and abstract, and 26 articles were assessed for eligibility based on their full text (Figure 1). Finally, 12 studies were included in the qualitative synthesis and 11 in the quantitative synthesis (meta-analysis).

### Characteristics of Included Studies

Total study population size of the studies included varied from 20 to 549 women (Table 1). In 11 out of the 12 included studies, women had undergone a prophylactic bilateral (salpingo-) oophorectomy or an oophorectomy for benign conditions (with or without hysterectomy). The remaining study included women 3–6 years after surgery for stage IA and IIB cervical carcinoma.<sup>25</sup> No RCTs or RCOTs were retrieved that included women after a risk-reducing salpingo-oophorectomy (RRSO). The inclusion period after surgery ranged from immediately after surgery until 27 years after surgery. In 10 out of 12 studies, BSO was performed at a premenopausal age in the majority of women included in the study, although most studies did not mention menopausal status at time of surgery. Seven studies were RCTs,<sup>20,26–31</sup> 5 studies had a randomized cross-over

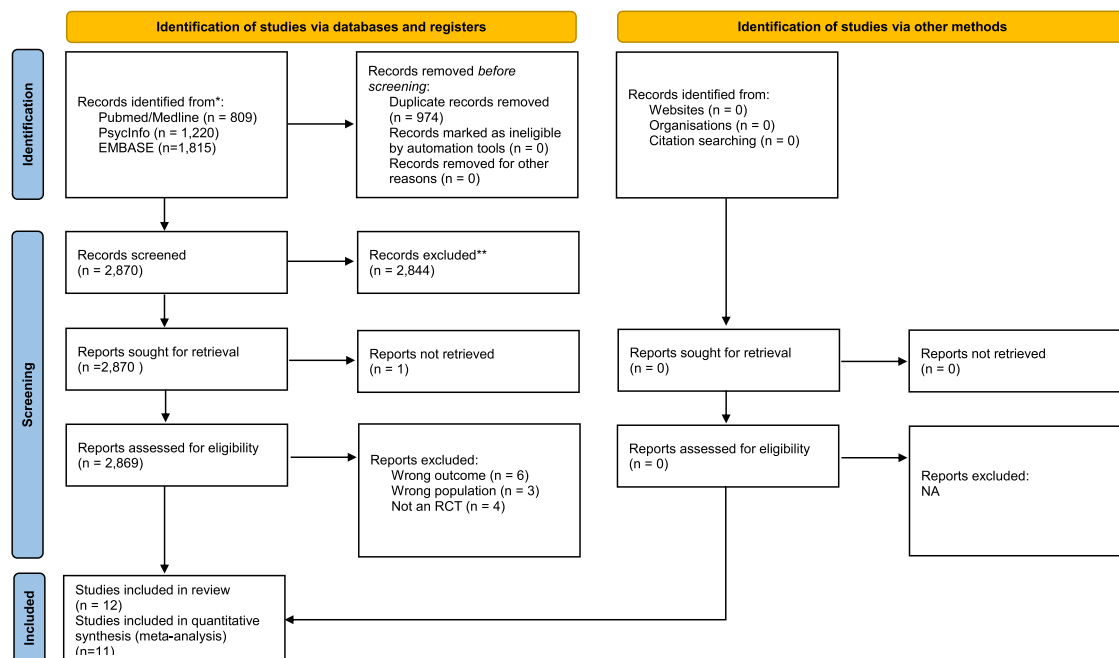


Figure 1. Flow diagram of study selection.

**Table 1.** Characteristics of studies included

Author, year, study design, country	Population N analyzed, mean age in yrs (SD)	Reason for oophorectomy Type of surgery Time since surgery	Intervention Type, administration, dose, length of use	Co-intervention Control-group	Outcomes Measured concept, scale	Time-point measurement (wks)
<b>ESTROGEN AND/OR TIBOLON</b>						
Baksu, 2005, RCT, TUR	N 65	BD BSO + HYS Within 6 wks	- Tibolon 2.5 mg/day, oral, 6 mo. - Transdermal estradiol, 3.9 mg/wk, 6 mo.	None Placebo	- HDRS - HARS	0, 26
Crona, 1988, COT, SWE	N 20 Age at surgery: 27-47	Stage IB/IIA cervical carcinoma Wertheim-Meigs surgery 3-6 years	- Tibolon 2.5 mg/day, oral, 6 wks - Estradiol valerate 2 mg/day, oral, 6 wks	None Placebo	- Mood ratings	0, 6
Dennerstein 1979, RCT, AU	N 28 Age: 46.2 (8.92)	BD BSO + HYS Median 2 yrs (range: 0.5-27 yrs)	- Etinyl oestradiol 50 µg/day, oral, 3 mo. - Levonorgestrel 250 µg/day, oral 3 mo. - Norgestrel 50 µg etinyl oestradiol + 250 µg levonorgestrel, oral 3 mo.	Estradiol valerate 2 mg Placebo	- HDRS - Verbal self-reports of general feelings - VAS: mood, tension, anxiety	0, 4, 8, 12
<b>ESTROGEN + ANDROGEN</b>						
Sherwin 1985a, COT, CAN	N 43 Age: 45.8 (3.3)	Premenopausal BD BSO + HYS Immediately after surgery	Monthly injection with: - Estradiol dienanthate 7.5 mg + estradiol benzoate 1.0 mg + testosterone enanthate 150 mg (Climacteron), 3 mo. - Estradiol valerate 10 mg (Delestrogen), 3 mo. - Testosterone enanthate 200 mg (Delatestryl), 3 mo.	None Placebo	- DMRS: subscale sexual functioning	0, 12
Sherwin 1985b, COT, CAN	N 43 Age: 45.8 (3.3)	BD BSO + HYS Immediately after surgery	Monthly injection with: - Climacteron, 3 mo. - Delestrogen, 3 mo. - Delatestryl, 3 mo.	None Placebo	- Menopausal index: psychological symptoms	0, 4, 8, 12
<b>TESTOSTERONE</b>						
Braunstein, 2005, RCT, US	N 318 Age: Co: 48.5 (7.4) 150 µg: 50.4 (8.0) 300 µg: 49.6 (7.9) 450 µg: 49.0 (7.5)	BD BSO At least 1 year	Transdermal testosterone, 150 µg, 300 µg or 450 µg daily Twice wks, 24 wks	Oral estrogen Placebo	- PFSF - PDS - SAL score	0, 24
Buster, 2005 RCT, US, CAN, AU	N 417 Age: Co: 49.5 (7.55) Int: 48.3 (7.45)	BD BSO + HYS At least 6 months	Transdermal testosterone patch, 300 µg daily Twice wks, 24 wks	Oral or trans-dermal estrogen Placebo	- PFSF - PDS - SAL score	0, 24
Davis, 2006, RCT, multi	N 61 Age: Co: 49.3 (range: 30-63) Int: 51.0 (range: 38-66)	BD BSO At least 1 year	Transdermal testosterone patch, 300 µg daily. Twice wks, 24 wks	Transdermal estrogen Placebo	- PFSF - SAL - PGWB	0, 12, 24
Flöter, 2002, COT, SWE	N 44 Age: 54.0 (2.9)	BD BSO + HYS Mean: 4.6 yrs (SD 2.4)	Testosterone undecanoate 40 mg/day, oral, 24 wks	Estradiol valerate, 2 mg Placebo	- PGWB - Self-esteem - McCoy's sex scale questionnaire	0, 24
Shifren, 2000, COT, US	N 65 Age: 47 (range: 31-56)	Premenopausal BD BSO + HYS Mean: 4.7 yrs (range: 1-10)	Transdermal testosterone, 150 µg or 300 µg. Twice wks, 12 wks	Conjugated equine estrogen, at least 0.625 mg Placebo	- BIFS-W - Telephone based diary: frequency of sexual thoughts, desires, and activities. - PGWB	0, 24 -4, 0, 9, 12

(continued)

Table 1. Continued

Author, year, study design, country	Population N analyzed, mean age in yrs (SD)	Reason for oophorectomy surgery; Time since surgery	Intervention Type, administration, dose, length of use	Co-intervention Control-group	Outcomes Measured concept, scale	Time-point measurement (wks)
Simon, 2005, RCT, US, CAN, AU	N 549 Age: Co: 48.9 (7.4) Int: 49.2 (7.7)	BD BSO + HYS At least 6 m. Mean: Co: 8.6 yrs (SD 6.6) Int: 8.7 yrs (SD 7.0)	Transdermal testosterone, 300 µg daily. Twice w/ky, 24 wks	Oral or transdermal estrogen Placebo	- SAL - PFSF - PDS	0, 4, 8, 12, 24
Warnock, 2005, RCT, US	N 100 Age: Co: 49.6 (6.6) Int: 48.1 (7.6)	Premenopausal BD BSO and/or HYS At least 3 mo. Mean: BSO: 6.9 yrs BSO + HYS: 7.4 yrs	Methyltestosterone, 2.5mg/day, oral, 8 wks	1.25mg esterified estrogens Placebo	- CSFQ-W - MSIQ - SES - WHQ	0, 4, 8

AE= adverse events; AU= Australia; BD= benign disorders; BISF- W= brief index of sexual functioning for women; BO= bilateral oophorectomy; BSO= bilateral salpingo-oophorectomy; CAN= Canada; COT= cross-over trial; Co= control group; CSFQ-W= changes in sexual functioning questionnaire - women; DMRS= daily menopause rating scale; HARS= hamilton anxiety rating scale; HDRS= hamilton depression rating scale; HYS= hysterectomy; Int= intervention group; Mo= months; MSIQ= menopausal sexual interest questionnaire; Multi= multinational; PDS= personal distress scale; PFSF= profile of female sexual functioning; PGWB= personal general well-being scale; RCT= randomized controlled trial; SAL= sexual activity log; SD= standard deviation; SES= Sexual Energy Scale; SWE= Sweden; TAH= total abdominal hysterectomy; TUR= Turkey; VAS= visual analogue scale; US= United States; WHQ= women's health questionnaire; Wk(s)= week

design.<sup>12,25,32–34</sup> The publishing year of included studies ranged from 1979 until 2006.

## sHRT and Primary Outcome

Included studies investigated the efficacy of estradiol, estradiol valerate, etinyl estradiol, estradiol dienanthate, tibolone, levonorgestrel, testosterone, testosterone enanthate, testosterone undecanoate, and methyltestosterone in comparison to a control intervention.<sup>20,25,30,32,33</sup> In [supplementary table B.1](#), administration type, dose, frequency, marketing status, and measures of bioavailability can be found for the included interventions. The aforementioned data were not available for all included interventions.

In nine studies, the efficacy of testosterone was studied compared to a control intervention.<sup>12,26–29,32–34</sup> Ten of the 12 included studies reported on the effects of sHRT on psychological well-being and the effects of sHRT on sexual functioning was investigated in 8 studies. Different scales were used to measure the same concepts. The scales used to measure psychological well-being and sexual functioning are reported in the appendix ([Table C.1](#)). Included studies assessed the effect on short term ( $\leq 12$  weeks) or medium term (12–26 weeks).

## Risk of Bias Assessment

For most studies, the risk of selection bias was designated as unclear/no information, because the randomization procedure was not described clearly. Due to high drop-out rates ( $\geq 20\%$ ), attrition bias was assessed as high in 5 of the 11 assessed studies.<sup>12,26,27,29,30</sup> Two articles from Sherwin et al. reported on separate outcome measures from the same study population and study design, therefore a combination assessment was performed for risk of bias for those 2 articles ([Table D.1](#), [Figure A.1](#)).<sup>32,33</sup>

## Meta-Analyses

Results from our analyses are presented in [Table 2](#). Data from before the cross-over were not available for the included studies, therefore separate analyses were performed for RCOTs and RCTs. For extracted data, see [Table E.1](#). For the transformed outcomes as used in the meta-analysis, see [table F.1](#). The results of our analyses are shown in [Figure 2a–c](#), but due to an insufficient number of high-quality studies, these should not be interpreted as true meta-analyses.

**Psychological Well-being.** A statistically significant benefit was seen from estradiol compared to control on depressed mood in a meta-analysis including 2 RCOTs on short to medium term (SMD: -1.37, 95%CI: -2.38 to -0.37,  $P = .007$ ). Heterogeneity was high (79%). One RCOT by Dennerstein et al.<sup>30</sup> investigated the effect of etinyl estradiol, levonorgestrel and a combination of etinyl estradiol and levonorgestrel on depressed mood compared to placebo on short term and showed a statistically significant benefit only for etinyl-estradiol.<sup>30</sup> A statistically significant



**Table 2.** (a) Meta-analyses for the effect of different types of hormone replacement therapy on psychological well-being (b) Meta analyses for the effect of testosterone on sexual functioning

Outcome	N of studies included	N total analyzed	SMD (95%CI)	P (overall effect)	I <sup>2</sup>	χ <sup>2</sup>	P (heterogeneity)
<b>ESTROGEN</b>							
Depressive symptoms	2 <sup>#</sup>	94	-1.37 [-3.38 to -0.37]	0.007	79%	4.73	0.03
<b>TESTOSTERONE</b>							
Depressed mood	2 <sup>#</sup>	218	-0.30 [-0.72 to 0.12]	0.12	58%	2.41	0.17
Overall well-being	2 <sup>#</sup>	218	-0.19 [-0.45 to 0.08]	0.17	0%	0.77	0.38
Anxiety	2 <sup>#</sup>	218	-0.14 [-0.40 to 0.13]	0.31	0%	0.99	0.42
Outcome	N of studies included	N total analyzed	SMD (95%CI)	P (overall effect)	I <sup>2</sup>	χ <sup>2</sup>	P (heterogeneity)
Satisfying activity	4 <sup>*</sup>	1189	0.39 (0.25 to 0.52)	<0.0001	22%	3.86	0.28
Overall functioning	2 <sup>#</sup>	218	0.38 (0.11 to 0.65)	0.006	0%	0.06	0.80
Sexual desire	5 <sup>*</sup>	1273	0.38 (0.19 to 0.56)	<0.0001	54%	8.63	0.07
Sexual desire	2 <sup>#</sup>	218	0.30 (0.03 to 0.56)	0.03	0%	0.49	0.48

\*Randomized controlled trials

#Randomized cross-over trials

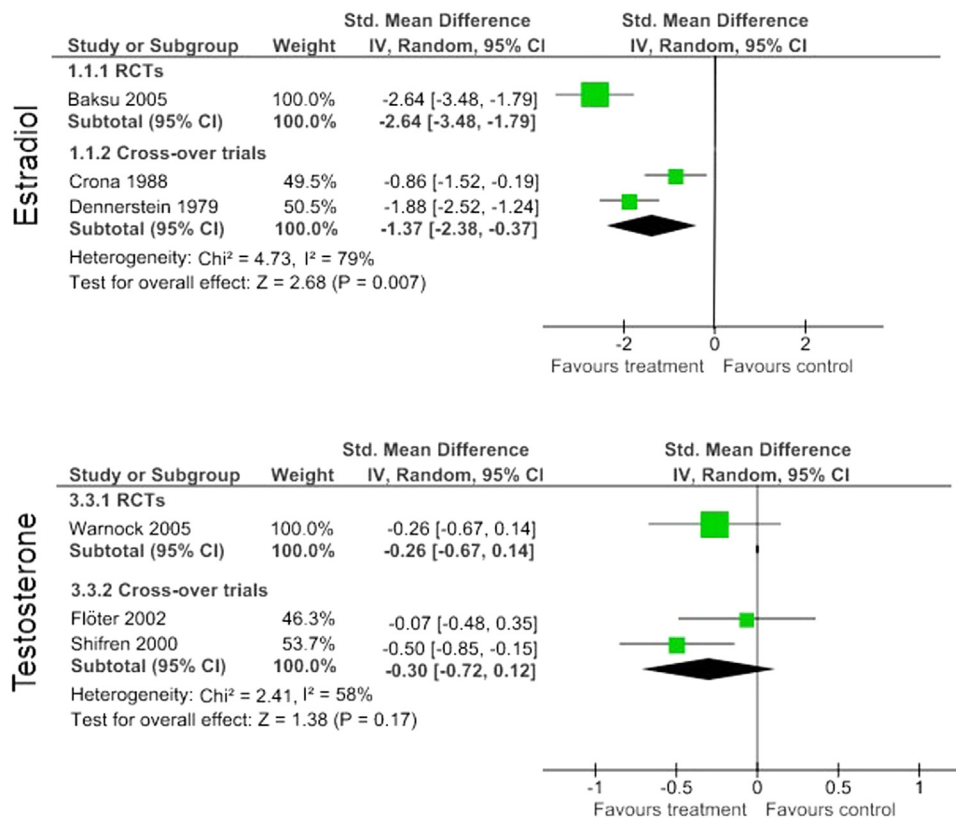
benefit was seen from tibolone compared to placebo on depressed mood in 1 RCT (Baksu et al)<sup>20</sup> and in 1 RCOT (Crona et al)<sup>25</sup> on short to medium term.

In a meta-analysis including two RCOTs, the effect of transdermal testosterone was not statistically significant on short term for depressed mood compared to placebo (SMD: -0.30, 95%CI:

-0.72 to 0.12, *P* = .17, *I*<sup>2</sup>: 58%), well-being (SMD: -0.19, 95%CI: -0.45 to 0.08, *P* = .17) and anxiety (SMD: -0.14, 95%CI: -0.40 to 0.13, *P* = .31).

**Sexual Functioning.** One study reported on the effects of monthly injection with estradiol valerate on sexual functioning

### Depressed mood



**Figure 2.** a: Forest plots for the effect of estradiol and testosterone on depressed mood, b: Forest plots for the effect of testosterone on sexual functioning, c: Forest plots for the effect of testosterone on psychological symptoms.

Testosterone

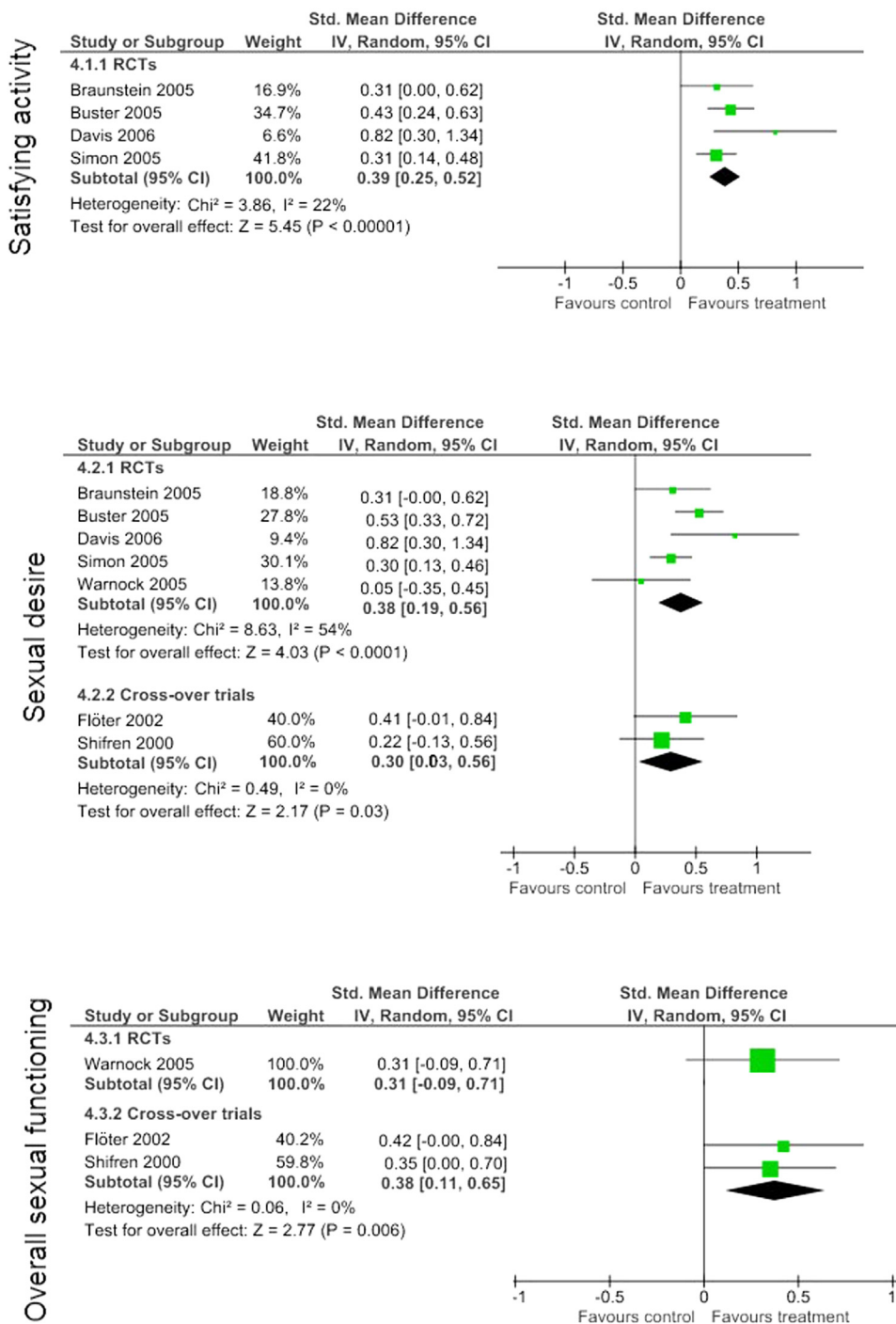


Figure 2 Continued.



## Testosterone

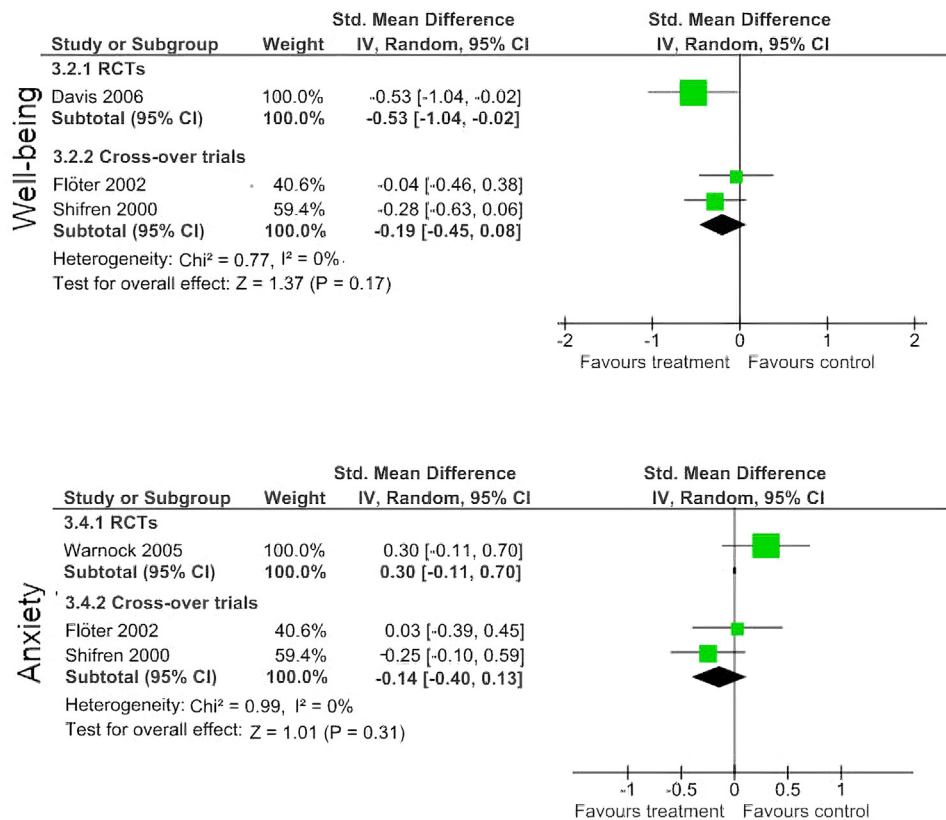


Figure 2. Continued

at 12 weeks (Sherwin 1985a).<sup>32</sup> This study did not show a statistically significant beneficial effect from estradiol valerate on sexual functioning in women with surgical menopause compared to placebo. Testosterone had a statistically significant beneficial effect on sexual desire on medium term when compared to placebo in a meta-analysis including 5 RCTs, (SMD: 0.38, 95%CI: 0.19–0.56,  $P < .0001$ ) and in a meta-analysis including 2 RCOTs (SMD: 0.30, 95%CI: 0.03–0.56,  $P = .03$ ). In a meta-analysis including 2 RCOTs, testosterone had a statistically significant beneficial effect on overall sexual functioning compared to placebo on medium term (SMD: 0.38, 95%CI: 0.11–0.65,  $P = .006$ ). In a meta-analysis including 4 RCTs, testosterone had a statistically significant beneficial effect on satisfying sexual activity compared to placebo on medium term (SMD: 0.39, 95%CI: 0.25–0.52,  $P < .0001$ ).

### Adverse Events

The number of adverse events and withdrawal due to adverse events were reported by 8 of the 12 included studies (Table G.1).<sup>12,26–30,34,31</sup> The difference in withdrawal rates due to adverse events between placebo and intervention groups was relatively small.

### Publication Bias and Subgroup Analyses

Publication bias could not be assessed, because there were less than 10 studies reporting on a comparable outcome within the same type of sHRT.<sup>24</sup> For the same reason, it was not possible to perform subgroup analyses.

### Funding

Eight of the 10 studies that reported funding sources<sup>12,26–30,32–34</sup> were funded by a pharmaceutical company (1 study investigating estrogen, 7 studies investigating testosterone), of which 5 studies were funded by Procter and Gamble Pharmaceuticals (Cincinnati, OH, USA (all investigating testosterone) (Table H.1).<sup>12,26–29</sup> In at least 3 of those studies, Procter and Gamble Pharmaceuticals were actively involved as co-author(s) and/or in statistical analyses.<sup>26–28</sup>

## DISCUSSION

### Main Findings

This systematic literature review including RCOTs and RCTs reported a benefit for depressed mood from estrogen with high heterogeneity. No benefit was seen for the effect of testosterone

on psychological symptoms. Only one study included investigated the effect of estrogen on sexual functioning, with no beneficial effect. A benefit was seen for testosterone on sexual desire and overall sexual functioning. The overall quality of studies included in this systematic literature review was moderate. Eight of the 10 studies that reported funding sources were funded by pharmaceutical companies.

## Interpretation

**Estrogen, and Psychological Well-being.** Estrogen alone improved depressed mood in surgically menopausal women based on 2 RCOTs (SMD:  $-1.37$ , 95%CI:  $-2.38$  to  $-0.37$ ,  $P = .007$ ). Both trials included small numbers (in total 48 women could be analyzed) and heterogeneity between the studies was high ( $I^2$ : 79). Therefore, our results should be interpreted with caution.

It is known that independent of menopausal status, estrogen has an effect on mood and mental state, by stimulating an increase in dopamine-2 receptors in the brain, a neurotransmitter with an important role in regulating mood and experiencing pleasure.<sup>35</sup> Furthermore, estrogen stimulates an increase in 5-hydroxytryptamine2a (5HT2A) binding sites in areas in the brain concerned with the control of mood, mental state, and emotion.<sup>36</sup> Therefore, it seems likely that estrogen-containing hormone replacement therapy may improve psychological well-being. However, randomized controlled clinical trials with larger study populations are necessary to draw valid conclusions on the effect of estrogen-containing sHRT on psychological well-being.

**Estrogen and Sexual Functioning.** The included RCT by Sherwin et al. investigated the effect of estrogen use on sexual functioning in 43 surgically menopausal women and did not find a beneficial effect.<sup>32</sup> A meta-analysis could not be performed. Results from non-randomized studies investigating the effect of sHRT on sexual functioning after bilateral oophorectomy are controversial. A cross-sectional study by Tucker et al. found that estrogen replacement reduced rates of sexual dysfunction in women after RRSO, as did Johansen et al. in a retrospective study.<sup>16,35</sup> Finch et al. and Vermeulen et al. performed prospective studies and reported that estrogen replacement positively influenced sexual functioning after RRSO.<sup>15,37</sup> However, Madalinska et al. did not find a difference between estrogen-users and non-users regarding overall sexual functioning after RRSO.<sup>13</sup> The above-mentioned studies however included women after RRSO, ie surgery to reduce the risk to develop ovarian cancer in women with a *BRCA* mutation, as opposed to the women included in the studies in this review, who underwent an oophorectomy for benign conditions. Estrogen could have an indirect effect on sexual functioning by decreasing vaginal atrophy, leading to less dyspareunia which might improve overall sexual functioning. However, the direct effect of systemic estrogen replacement on sexual functioning after surgical menopause is still debatable.

**Testosterone and Psychological Well-being.** The current meta-analysis including two COTs reported that testosterone did not significantly affect psychological well-being, anxiety, or depressed mood in surgically menopausal women (SMD:  $-0.19$ , 95%CI:  $-0.45$  to  $0.08$ ; SMD:  $-0.14$ , 95%CI:  $-0.14$  to  $0.13$ ; SMD  $-0.30$ , 95%CI:  $-0.72$  to  $0.12$ ; respectively). Biologically, a beneficial effect of testosterone on psychological well-being seems plausible: testosterone is known for its enhancing effect on dopamine release and serotonin function in the brain.<sup>38,39</sup> Although the exact mechanisms are not yet fully understood, testosterone may influence serotonin function by its conversion into estradiol, which would mean that estrogen alone could have a similar or even larger beneficial effect than testosterone on depressed mood and well-being.<sup>40</sup> A one-armed study by Glaser et al. reported an improvement in psychological symptoms after subcutaneous testosterone implantation in natural postmenopausal women.<sup>41</sup> However, reliable evidence from larger human trials is still lacking.

**Testosterone and Sexual Functioning.** Testosterone had a beneficial effect on overall sexual functioning (SMD:  $0.38$ , 95%CI:  $0.11$ – $0.65$ ) as well as on sexual desire (SMD:  $0.38$ , 95%CI:  $0.19$ – $0.56$ ; SMD:  $0.30$ , 95%CI:  $0.03$ – $0.56$ ) and satisfying sexual activity (SMD:  $0.39$ , 95%CI:  $0.15$ – $0.52$ ), when compared to placebo. Somboonporn et al. conducted a systematic review on the effect of testosterone in women with menopause from all causes and found results similar to ours in their fixed analyses for the number of satisfying events, sexual desire and overall sexual functioning.<sup>42</sup> However, up until now, testosterone is not yet approved by the Food and Drug Administration (FDA) to improve sexual functioning in postmenopausal women due to a lack of (long-term) safety data.<sup>43</sup>

The testosterone patch *Intrinsa* was authorized by the European Medicines Agency (EMA) in 2006 for use in surgically menopausal women who concomitantly used estrogen, but in 2012 authorization was withdrawn by the company 'for commercial reasons'. Long-term safety data on breast cancer risk during and after testosterone use have been reported by very few studies, which is of particular importance for *BRCA1/2* mutation carriers, who have an increased risk of breast cancer. These women report moderate to severe psychosexual menopausal symptoms on the long-term,<sup>4-8</sup> but may be less willing to try 'new' pharmaceuticals because of their already increased breast cancer risk.

In postmenopausal women with increased testosterone levels, an increased breast cancer risk was reported by Key et al.<sup>44</sup> Additionally, the Women's Health Initiative study found an increased risk of invasive breast cancer for Estratest users (1.25 mg esterified estrogens with 2.5 mg methyltestosterone, adjusted hazard ratio:  $1.78$ , 95%CI  $1.05$ – $3.01$ ), although the risk was not statistically significantly elevated when all types of hormonal replacement treatments containing both estrogen and testosterone were included in the analysis (HR  $1.42$ , 95%CI  $0.95$ – $2.11$ ).<sup>45</sup> Nonetheless, as a result doctors might have been hesitant to prescribe testosterone, which may have contributed to the withdrawal of

testosterone from the pharmaceutical market in Europe, but this is all speculation.

### The Involvement of Pharmaceutical Companies

The involvement of pharmaceutical companies in at least 8 of the 12 included studies could potentially have threatened the independency of the results of these studies. Procter & Gamble Pharmaceuticals funded 5 out of the 7 included studies, all investigating the effect of testosterone on sexual functioning. They were involved in data analysis and/or writing the manuscript in at least 3 of the 7 studies. The rationale for withdrawing testosterone from the European market for the purpose of treating sexual symptoms in women is not publicly available.

### Strengths

To the best of our knowledge, this is the first systematic review investigating the effect of different types of sHRT including testosterone on sexual functioning and psychological well-being in surgically menopausal women. In addition, the current systematic review only included studies that investigated patient-reported outcomes. Therefore, the results reflect perceived well-being and sexual functioning, and not simply objectively experienced menopausal symptoms.

### Limitations

The most important limitation is the small number of randomized studies eligible to be included in this systematic review for estrogen replacement therapy and estrogen-progesterone replacement therapy. Consequently, for some outcomes it was not possible to perform a meta-analysis because only one included study investigated this specific outcome for a specific type of sHRT and it was not possible to perform sensitivity analyses or to assess publication bias. Moreover, the most up-to-date RCT was published in 2006, which is 16 years ago. The authors did an extensive literature search and did not find more recent RCTs. The reason behind this may be the Habits trial, which was prematurely stopped in 2004. This open-labeled RCT included women who recovered from breast cancer and found a relative risk of 3.5 (95%CI 1.5–8.1) to develop a new breast cancer, which is why the safety and monitoring committee stopped the study. However, the impact of acute surgical menopause on quality of life and sexual functioning is immense and might make it commercially attractive to market medication for this.<sup>5,46,47</sup>

Studies included were often small and of moderate quality. In 7 out of 11 studies, allocation concealment was considered unclear, which might have exaggerated effect estimates.<sup>48,49</sup> Furthermore, varying lengths of follow-up, different routes of administration, different pharmaceutical forms different types of questionnaires to measure the same concepts, unknown menopausal status and varying reasons for undergoing BSO contributed to the clinical diversity of the studies included, which might have caused the moderate to high heterogeneity found in our analyses. However,

we do not consider the differences in effects between different formulations and routes of administration as a limitation, because our aim was to investigate the effect of sHRT as a group.

### Conclusions and Implications

Estrogen and estrogen-progesterone may improve symptoms of depression in surgically menopausal women. However, the effect of estrogen on sexual symptoms after surgical menopause has not been conclusively established. Testosterone seems to improve sexual desire and overall sexual functioning in surgically menopausal women, although the drug is not FDA approved and has been withdrawn from EMA approval 'for commercial reasons'. Independent, well-designed intervention studies are urgently needed to establish efficacy and safety of estrogen and testosterone replacement therapy in surgically menopausal women, to justify (or stop) its prescription (off-label) for treating psychosexual symptoms. Clinicians counseling women after surgical menopause on the use of sHRT could use these results in the process of matching expectations and shared-decision making on hormone replacement options. The (re)marketing of testosterone should be delayed until long-term safety data are available, specifically regarding breast cancer risk in addition to research that focuses on women's motivation to start and stop using it. This is of particular importance for *BRCA1/2* mutation carriers with a history or increased risk of breast cancer.

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## SUPPLEMENTARY MATERIALS

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