



Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data

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Summary

Background The benefits and risks of testosterone treatment for women with diminished sexual wellbeing remain controversial. We did a systematic review and meta-analysis to assess potential benefits and risks of testosterone for women.

Methods We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science for blinded, randomised controlled trials of testosterone treatment of at least 12 weeks' duration completed between Jan 1, 1990, and Dec 10, 2018. We also searched drug registration applications to the European Medicine Agency and the US Food and Drug Administration to identify any unpublished data. Primary outcomes were the effects of testosterone on sexual function, cardiometabolic variables, cognitive measures, and musculoskeletal health. This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42018104073.

Findings Our search strategy retrieved 46 reports of 36 randomised controlled trials comprising 8480 participants. Our meta-analysis showed that, compared with placebo or a comparator (eg, oestrogen, with or without progestogen), testosterone significantly increased sexual function, including satisfactory sexual event frequency (mean difference 0.85, 95% CI 0.52 to 1.18), sexual desire (standardised mean difference 0.36, 95% CI 0.22 to 0.50), pleasure (mean difference 6.86, 95% CI 5.19 to 8.52), arousal (standardised mean difference 0.28, 95% CI 0.21 to 0.35), orgasm (standardised mean difference 0.25, 95% CI 0.18 to 0.32), responsiveness (standardised mean difference 0.28, 95% CI 0.21 to 0.35), and self-image (mean difference 5.64, 95% CI 4.03 to 7.26), and reduced sexual concerns (mean difference 8.99, 95% CI 6.90 to 11.08) and distress (standardised mean difference -0.27, 95% CI -0.36 to -0.17) in postmenopausal women. A significant rise in the amount of LDL-cholesterol, and reductions in the amounts of total cholesterol, HDL-cholesterol, and triglycerides, were seen with testosterone administered orally, but not when administered non-orally (eg, by transdermal patch or cream). An overall increase in weight was recorded with testosterone treatment. No effects of testosterone were reported for body composition, musculoskeletal variables, or cognitive measures, although the number of women who contributed data for these outcomes was small. Testosterone was associated with a significantly greater likelihood of reporting acne and hair growth, but no serious adverse events were recorded.

Interpretation Testosterone is effective for postmenopausal women with low sexual desire causing distress, with administration via non-oral routes (eg, transdermal application) preferred because of a neutral lipid profile. The effects of testosterone on individual wellbeing and musculoskeletal and cognitive health, as well as long-term safety, warrant further investigation.

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Introduction

No international consensus exists to guide use of testosterone in women. Nonetheless, clinicians have treated women with various forms of testosterone for decades, primarily for diminished sexual wellbeing.¹ Previous systematic reviews of testosterone treatment for women have indicated favourable effects on sexual function,^{2,3} but these analyses have included scant data for safety or adverse effects. We did a systematic review and meta-analysis of randomised controlled trials that reported the effects of systemic testosterone treatment compared with placebo or a comparator (eg, oestrogen, with or without progestogen) on sexual function,

cardiometabolic variables, cognitive measures, and musculoskeletal health, including previous unpublished data.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁴ We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science using Ovid software. The full search strategy and keywords used have been published elsewhere.⁵

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Research in context

Evidence before this study

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science for randomised controlled trials of testosterone in women published between Jan 1, 1990, and Dec 10, 2018, and drug registration applications to the European Medicine Agency and the US Food and Drug Administration in the same period. The search was restricted to the English language and the search terms were as published in PROSPERO (CRD42018104073). Older systematic reviews indicate testosterone therapy has favourable effects on female sexual function. The most recent systematic review, published in 2017, was restricted to use of transdermal testosterone. Unpublished trials and those that did not provide sufficient data were not included in previous reviews.

Added value of this study

Our systematic review and meta-analysis includes data for all modes of testosterone administration (oral and non-oral) and complete data from randomised controlled trials not included in earlier reviews or that remain unpublished. Our meta-analysis

shows that testosterone supplementation improves sexual function in naturally and surgically postmenopausal women, whether or not they are using concurrent oestrogen. The findings of our study reaffirm that only non-oral testosterone should be prescribed because of the adverse lipoprotein effects of oral testosterone. Data are insufficient to draw conclusions about the effects of testosterone on musculoskeletal, cognitive, and mental health and long-term safety and use in premenopausal women.

Implications of all the available evidence

Non-oral testosterone treatment is effective for postmenopausal women presenting with low sexual desire that causes them personal concern. Available data do not support use of testosterone in premenopausal women, and testosterone should not be used to treat depression or bone loss or to prevent cognitive decline. To safely prescribe testosterone for low sexual desire, formulations for women are needed because, at present, only male formulations resulting in testosterone concentrations several fold greater than appropriate for women, and compounded testosterone, are available.

We also searched drug registration applications to the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA).

The final search results were restricted to studies completed between Jan 1, 1990, and Dec 10, 2018. Inclusion criteria for studies were that they should be randomised clinical trials, have a duration of systemic testosterone treatment of at least 12 weeks, be at least single blind (ie, participants and assessors had to be unaware of the intervention or interventions), and have a placebo or comparator arm (eg, oestrogen, with or without progestogen). Participants could be aged 18–75 years and be premenopausal or postmenopausal. No restriction was placed on type of menopause (natural or surgical), use of concurrent hormone treatment (oestrogen with or without progestogen), or publication language. Studies of intravaginal testosterone were excluded.

Studies were selected in a two-stage process. First, titles and abstracts from the electronic searches were scrutinised by two independent reviewers (RMI and RJB). Second, if the abstract met inclusion criteria we obtained full reports and final decisions were made about study inclusion. Disagreement between reviewers about inclusion or exclusion of a particular report was resolved by discussion between the review team (RMI, RJB, and SRD). Corresponding authors of reports selected for inclusion were contacted for further details if data were incomplete or unclear. Amgen (Thousand Oaks, CA, USA) approved the inclusion of data pertaining to randomised controlled trials of a testosterone patch from documents submitted to the EMA⁶ and the FDA.⁷

These documents provided details and outcomes of two unpublished randomised controlled trials that were done under the FDA's Investigational New Drug programme, as well as precise sample sizes and SEs not included in published papers. In two instances, data were only available as combined studies and, hence, were included in this manner.

Procedures

Two reviewers (RMI and RJB) independently extracted data for participants' characteristics, interventions, and study outcomes. A pro-forma—designed by the review team—was used and included study characteristics for author and year, study location and setting, menopausal status, age, sample size, type of treatments used, mode of administration, dose administered, duration of treatment, and outcomes measured.

A transdermal patch releasing 300 µg of testosterone per day achieved amounts of free testosterone in blood in the upper end of the premenopausal range.⁸ Therefore, only outcomes for the 300 µg releasing patch were used for any studies that included lower or higher dose patches. For any studies that assessed other modes of testosterone delivery, outcomes for the dose that resulted in amounts of testosterone in blood closest to those seen with the 300 µg patch were used.

The Cochrane risk-of-bias tool⁹ was used to assess random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and

other biases. Risk of bias was assessed by two of us (RMI and RJB) independently, except for seven trials in which SRD was a co-author, in which case the risk of bias was assessed by MJP. Disagreements were resolved by consensus or by consultation with a third individual (SRD or SG).

Outcomes

The primary outcomes included the effects of testosterone on sexual function (ie, sexual events, total sexual function scores, and scores for sexual desire, arousal, orgasm, pleasure, concerns, responsiveness, sexual self-image, and sexual distress), cardiometabolic variables (ie, weight, BMI, waist-to-hip ratio, systolic and diastolic blood pressure, measures of glucose intolerance, high-sensitivity C-reactive protein, and lipids), cognitive performance and cognitive fatigue, and musculoskeletal health (ie, bone mineral density, body composition, and muscle strength). Secondary outcomes included serious adverse events, androgenic effects, breast effects, mood and wellbeing, and study withdrawal.

Statistical analysis

Studies were grouped according to the mode of testosterone administration (oral or non-oral), menopausal status (postmenopausal or premenopausal), type of menopause (natural or surgical), mode of concurrent oestrogen delivery (oral or non-oral), outcome measured, and trial duration (12 months or >12 months if data were available). For studies that used the same assessment method and provided continuous data we reported mean difference, and for those that used different methods we reported the standardised mean difference, using the inverse-variance method. For dichotomous data, we used the number of events in the control and intervention groups of every study to calculate the Mantel-Haenszel risk ratio (RR). Outcomes from individual studies were pooled using a random-effects model, because this approach assumes that there could be clinical and methodological heterogeneity that might affect the findings. All pooled analyses were reported with 95% CIs. The DerSimonian and Laird method of moments estimator was used to estimate the between-study variance, and 95% CIs were calculated using the Wald type method.¹⁰ Heterogeneity of exposure effects was assessed using the I^2 statistic. Prediction intervals were calculated for sexual outcomes with high I^2 values ($I^2 > 50\%$), which indicated variability in the treatment effect was attributable to study heterogeneity not chance.¹¹ The χ^2 test for heterogeneity was also done. We judged a p value less than 0.05 significant. Subgroup analyses were done to assess the potential contribution of differences in menopausal status and mode of testosterone administration. When more than ten studies were included in an outcome analysis, contour enhanced funnel plots were created to investigate small study effects, which can result from reporting biases, methodological or clinical

heterogeneity, or other factors.¹² When data were only available as graphs in published papers, we used DigitizeIt software version 2.3¹³ to extract the required data from the graphs. Furthermore, we imputed missing SDs of means for some studies using SEs, 95% CIs, or p values. We adhered to published guidance of the Cochrane handbook¹⁴ throughout. We used the *metan* command in Stata version 15 (StataCorp, College Station, TX, USA) to do random effects meta-analyses.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

A PRISMA flowchart of study selection is presented in figure 1. The overall search resulted in 6491 citations. 2651 duplicate studies were excluded; a further 3769 studies were excluded on review of title and abstract, and 25 reports did not meet inclusion criteria. Thus, 46 publications from 36 randomised controlled trials

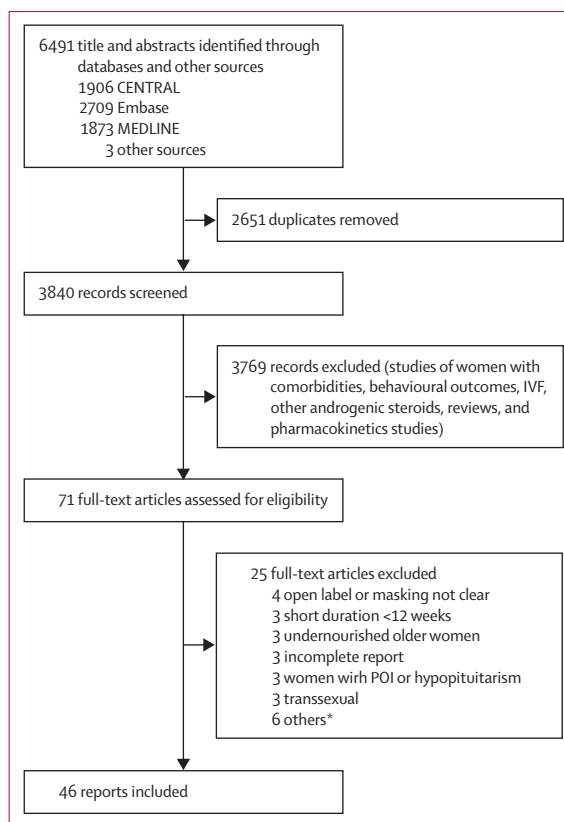


Figure 1: Selection of studies for inclusion

CENTRAL=Cochrane Central Register of Controlled Trials. POI=primary ovarian insufficiency. IVF=in-vitro fertilisation. *Studies were excluded because they were either a review, protocol, non-randomised controlled trial, or had no appropriate comparators.

	Country	Setting	Study population	Primary outcomes of study	Age range or mean age (years)	Women randomised (n)	Study duration	Route of administration	Interventions
Barrett-Connor et al (1999) ¹⁵	USA	Multicentre	Surgical menopause	Bone mineral density and lipids	21–65	311	2 years	Oral	Conjugated equine oestrogen 0.625 mg or 1.25 mg daily; conjugated equine oestrogen 0.625 mg plus methyltestosterone 1.25 mg daily; or conjugated equine oestrogen 1.25 mg plus methyltestosterone 2.5 mg daily
Basaria et al (2002) ¹⁶	USA	Single centre	Surgical menopause and natural menopause on oestrogen therapy	Plasma viscosity and fibrinogen	42–77	40	16 weeks	Oral	Esterified oestrogen 1.25 mg daily with or without methyltestosterone 2.5 mg daily
Braunstein et al (2005) ¹⁷	USA	Multicentre	Surgical menopause with low sexual desire	Sexual function	24–70	447	24 weeks	Patch	Conjugated equine oestrogen daily plus transdermal testosterone patch 150 µg, 300 µg, or 450 µg twice weekly; or placebo
Buster et al (2005) ¹⁸	Australia, Canada, and USA	Multicentre	Surgical menopause with low sexual desire	Sexual function	≥20	533	24 weeks	Patch	Conjugated equine oestrogen plus testosterone patch 300 µg twice weekly; or placebo
Davis et al (1995, ²² 2000) ^{24*†}	Australia	Single centre	Surgical menopause and natural menopause	Sexual function	51.3 (oestradiol), 57.0 (testosterone)	34	2 years	Implant	Oestradiol 50 mg every 3 months with or without testosterone 50 mg every 3 months
Davis et al (2006) ²³	Australia and Europe	Multicentre	Surgical menopause with low sexual desire	Sexual function	20–70	77	24 weeks	Patch	Testosterone patch 300 µg daily; or placebo
Davis et al (2008a) ¹⁹	Australia	Multicentre	Premenopausal women with low sexual desire	Sexual function	35–46	261	16 weeks	Spray	Testosterone spray 56 µL, 90 µL, or 180 µL (50 µg/µL) daily; or placebo
Davis et al (2008b, ⁸ 2009) ^{20†}	Multinational	Multicentre	Surgical menopause and natural menopause with low sexual desire	Sexual function	20–70	814	52 weeks	Patch	Testosterone patch 150 µg or 300 µg daily; or placebo
Davis et al (2014) ²¹	Australia	Single centre	Natural menopause	Cognition	55–65	89	26 weeks	Gel	Transdermal testosterone gel 300 µg daily; or placebo
de Paula et al (2007) ²⁵	Brazil	Single centre	Natural menopause with sexual dysfunction	Sexual function	49–63	85	4 months	Oral	HRT plus either methyltestosterone 2.5 mg daily or placebo
Dias et al (2006) ²⁶	Brazil	Multicentre	Natural menopause with depression	Depression	53.7	72	24 weeks	Oral	Oestradiol 0.625 mg, medroxyprogesterone acetate 2.5 mg, and methyltestosterone 2.5 mg daily; oestradiol 0.625 mg, medroxyprogesterone 2.5 mg, and placebo daily; methyltestosterone 2.5 mg and two placebos daily; or three placebos daily
Dobs et al (2002) ²⁷	USA	Single centre	Surgical menopause and natural menopause	Body composition	41–76	40	16 weeks	Oral	Esterified oestrogen 1.25 mg daily with or without methyltestosterone 2.5 mg
El-Hage et al (2007) ²⁸	Australia	Single centre	Surgical menopause with low sexual function	Sexual function	54.0	36	12 weeks	Cream	Testosterone 10 mg cream daily; or placebo
Floter et al (2002, ³⁰ 2004, ³¹ 2005) ²⁹ and Kocoska-Maras et al (2009) ^{42†}	Sweden	Single centre	Surgical menopause	Sexual function	45–60	50	24 weeks	Oral	Oestradiol valerate 2 mg with or without testosterone undecanoate 40 mg daily
Fooladi et al (2014) ³²	Australia	Single centre	Women on SSRI or SNRI therapy and low sexual desire	Sexual function	35–55	44	12 weeks	Patch	Transdermal testosterone patch 300 µg daily; or placebo
Goldstat et al (2003) ³³	Australia	Single centre	Premenopausal women with low sexual desire	Sexual function	30–45	49	12 weeks	Cream	Testosterone 10 mg cream daily; or placebo
Gruber et al (1998) ³⁴	Austria	Single centre	Surgical menopause, no HRT	Body composition	51.4	39	6 months	Gel	2.5 g androstanolone twice daily; or placebo
Hickok et al (1993) ³⁵	USA	Single centre	Natural menopause	Lipids and menopausal symptoms	40–60	26	6 months	Oral	Esterified oestrogen 0.625 mg with or without methyltestosterone 1.25 mg daily

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	Country	Setting	Study population	Primary outcomes of study	Age range or mean age (years)	Women randomised (n)	Study duration	Route of administration	Interventions
(Continued from previous page)									
Hofling et al (2007a, ³⁶ 2007b) ^{37†}	Sweden	Single centre	Natural menopause	Breast density and cell proliferation	45–65	99	6 months	Patch	Conjugated equine oestrogen 2 mg and norethisterone acetate 1 mg plus testosterone 300 µg twice weekly; or conjugated equine oestrogen 2 mg and norethisterone acetate 1 mg plus placebo
Huang et al (2014a, ³⁸ 2014b, ⁴⁰ 2015a, ³⁹ 2015b) ^{41†}	USA	Two centres	Surgical menopause and natural menopause with total testosterone <31 ng/dL or free testosterone <3.5 pg/mL	Sexual function	21–60	71	24 weeks	Intra-muscular injection	Testosterone enanthate 3 mg, 6.25 mg, 12.5 mg, or 25 mg weekly; or placebo
Leao et al (2006) ⁴³	Brazil	Two centres	Surgical menopause	Cardiometabolic biomarkers	42–62	37	12 months	Oral	Oestradiol 1 mg plus either methyltestosterone 1.25 mg daily or placebo
Liu et al (2011) ⁴⁴	USA	Not clear	Natural menopause with 50 hot flushes per week	Vasomotor symptoms	Not clear	1248	12 weeks	Oral	Esterified oestrogen 0.15 mg, 0.30 mg, or 0.45 mg daily; esterified oestrogen 0.15 mg plus methyltestosterone 0.15 mg or 0.30 mg daily; esterified oestrogen 0.30 mg plus methyltestosterone 0.30 mg or 0.60 mg daily; methyltestosterone 0.60 mg daily; or placebo
Lobo et al (2003) ⁴⁵	USA	Multicentre	Surgical menopause and natural menopause with low sexual desire	Sexual function	45–65	218	16 weeks	Oral	Esterified oestrogen 0.625 mg with or without methyltestosterone 1.25 mg daily
Miller et al (2000) ⁴⁶	USA	Single centre	Surgical menopause and natural menopause	Bone mineral density and bone turnover markers	53.5 (oestradiol), 54.6 (testosterone)	66	12 weeks	Sub-lingual	Patients with hysterectomy: micronised oestradiol 0.5 mg with or without micronised testosterone 1.25 mg twice daily; patients with intact uterus: micronised oestradiol 0.5 mg plus micronised progesterone 100 mg with or without micronised testosterone 1.25 mg twice daily
Moller et al (2010, ⁴⁷ 2013) ^{48†}	Sweden	Single centre	Surgical menopause	Cognitive fatigue	45–60	50	24 weeks	Oral	Oestradiol valerate 2 mg plus either testosterone undecanoate 40 mg or placebo daily
Nathorst-Boos et al (2006) ⁴⁹	Sweden	Single centre	Natural menopause, on HRT with low sexual desire	Sexual function	50–65	60	3 months	Oral and trans-dermal	Testosterone 10 mg daily; or placebo
Panay et al (2010) ⁵⁰	Australia, Canada, Germany, and UK	Multicentre	Natural menopause with low sexual desire	Sexual function	40–70	272	6 months	Patch	Transdermal testosterone patch 300 µg twice weekly; or placebo
Penteado et al (2009) ⁵¹	Brazil	Single centre	Natural menopause with sexual complaints	Sexual function	42–60	60	12 months	Oral	Conjugated equine oestrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg plus either methyltestosterone 2.0 mg or placebo daily
Shifren et al (2000) ⁵²	USA	Multicentre	Surgical menopause with low sexual function	Sexual function	31–56	75	12 weeks	Oral and patch	Conjugated equine oestrogen 0.625 mg with or without testosterone 150 mg or 300 mg daily
Shifren et al (2006) ⁵³	Australia, Canada, and USA	Multicentre	Natural menopause with low sexual desire	Sexual function	40–70	549	24 weeks	Patch	Testosterone patch 300 µg twice weekly; or placebo
Simon et al (1999) ⁵⁵	USA	Multicentre	Natural menopause with menopausal symptoms	Somatic menopausal symptoms	53.7	93	12 weeks	Oral	Esterified oestrogen 0.625 mg or 1.25 mg daily; or esterified oestrogen 0.625 mg plus methyltestosterone 1.25 mg daily; or esterified oestrogen 1.25 mg plus methyltestosterone 2.5 mg daily; or placebo
Simon et al (2005) ⁵⁴	Australia, Canada, and USA	Multicentre	Surgical menopause with low sexual desire	Sexual function	20–70	562	24 weeks	Patch	Transdermal or oral oestrogen with transdermal testosterone patch or placebo
Watts et al (1995) ⁵⁶	USA	Multicentre	Surgical menopause	Bone mineral density and lipids	21–60	66	2 years	Oral	Esterified oestrogen 1.25 mg with or without methyltestosterone 2.5 mg daily
Wisniewski et al (2002) ⁵⁷	USA	Single centre	Surgical menopause and natural menopause	Cognitive function	46–77	26	4 months	Oral	Esterified oestrogen 1.25 mg with or without methyltestosterone 2.5 mg daily

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Country	Setting	Study population	Primary outcomes of study	Age range or mean age (years)	Women randomised (n)	Study duration	Route of administration	Interventions	
(Continued from previous page)									
Unpublished trial 2002005 (2004) ⁷	Australia, Canada, and USA	Multicentre	Natural menopause	Sexual function	40–70	610	52 weeks	Patch	Transdermal testosterone patch 300 µg daily; or placebo
Unpublished trial 2007004 (2011) ⁵⁸	USA	Multicentre	Natural menopause	Endometrial safety	45–70	1271	52 weeks	Patch	Transdermal testosterone patch 300 µg daily; or placebo

HRT=hormone replacement therapy. SSRI=selective serotonin reuptake inhibitor. SNRI=serotonin noradrenalin reuptake inhibitor. *Single-blind trial. †Same trial but yielded multiple publications with different outcomes.

Table: Characteristics of included trials

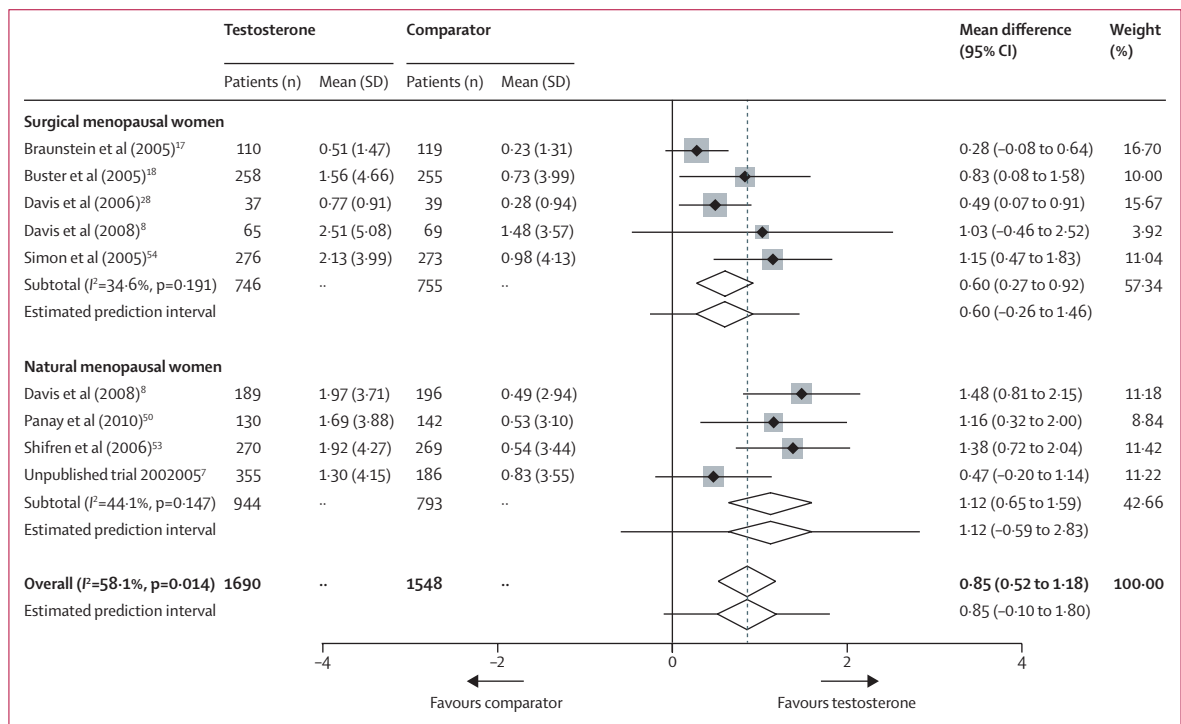


Figure 2: Effect of testosterone versus comparator on satisfying sexual events, by menopausal status

Data are change in number of satisfactory sexual events per month. Grey square indicates the weight of the study. Black diamond represents the mean difference per study and white diamond the mean difference overall. Horizontal lines depict the 95% CI. Vertical dotted line shows overall mean difference.

were included in the meta-analysis. 44 reports^{8,15–57} were identified by electronic searches and two^{7,58} were unpublished trials identified by manual searching. 13 studies specifically recruited women with low sexual function and one study recruited women based on the amount of testosterone in blood (table). Data included in the meta-analysis are from 8480 participants in 43 publications^{7,8,15–18,20–31,34–58} of postmenopausal women, two reports^{19,33} of premenopausal women, and one study³² that included both premenopausal and postmenopausal women. Testosterone was administered orally in 15 trials,^{7,15,16,25–27,30,35,43–45,47,51,55–58} non-oral administration was by transdermal patch in 13 trials,^{8,17–19,23,32,49,50,52–54}

transdermal cream in two trials,^{28,33} transdermal gel in two trials,^{21,34} transdermal spray in one trial,¹⁹ a sublingual formulation in one trial,⁴⁶ intramuscular injection in one trial,³⁸ and subcutaneous implant in one trial.²²

15 studies^{7,8,17,18,23,25,28,30,38,45,50–54} in 3766 postmenopausal women and three studies^{19,32,33} in 226 premenopausal women provided data for the effects of testosterone on sexual function (appendix pp 1, 2). Eight studies^{7,8,17,18,23,50,53,54} reported on the mean change in satisfying sexual events over 4 weeks; four studies included women who had surgical menopause, three included those in natural menopause, and one included both. In postmenopausal women, compared with placebo or a comparator,

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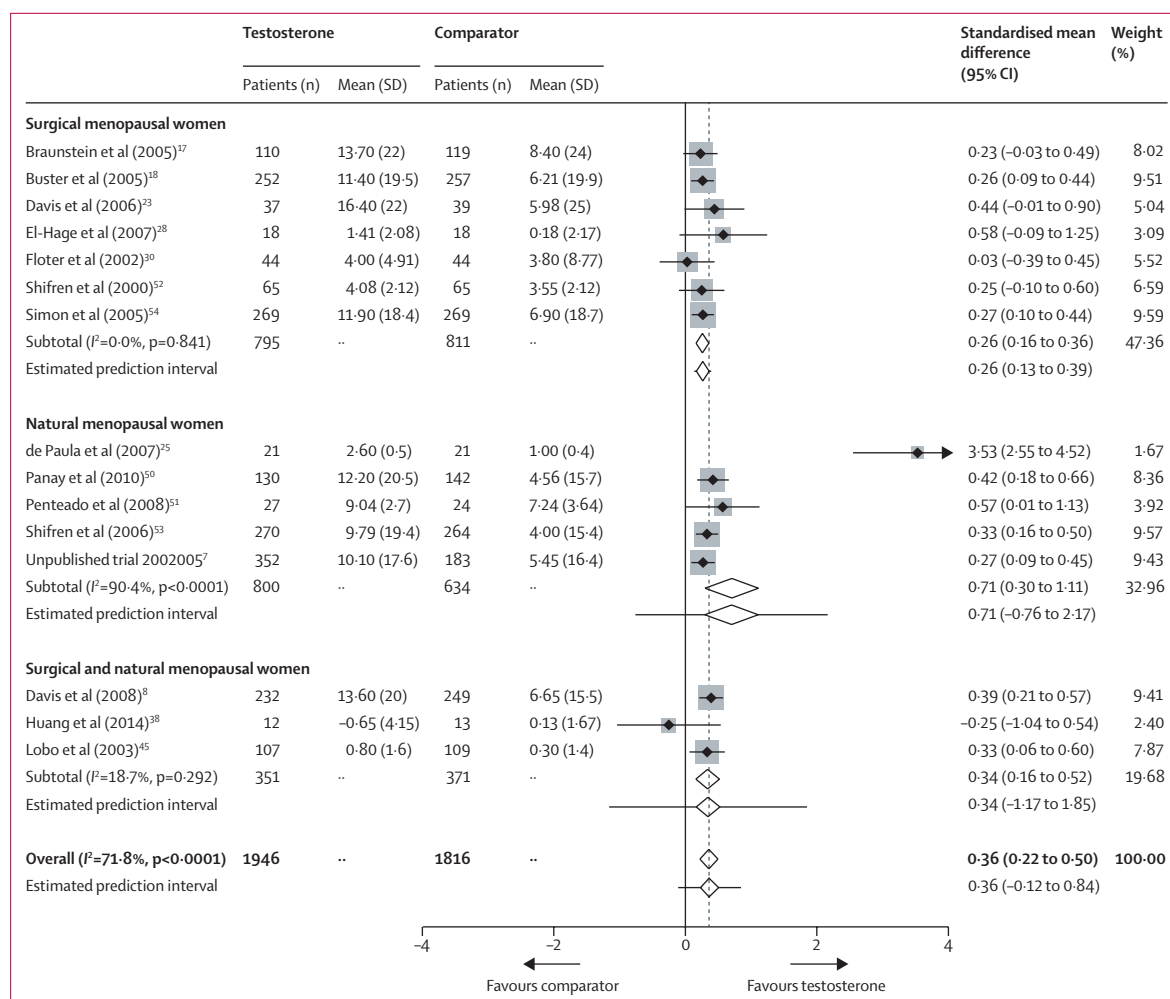


Figure 3: Effect of testosterone versus comparator on sexual desire, by menopausal status

Data are change in sexual desire score per month. Grey square indicates the weight of the study. Black diamond represents the standardised mean difference per study and white diamond represents the overall standardised mean difference. Horizontal lines depict the 95% CI. Vertical dotted line shows overall standardised mean difference.

testosterone was associated with a significant increase in the number of satisfying sexual events (mean difference 0.85, 95% CI 0.52 to 1.18; $p=0.014$; 95% prediction interval -0.10 to 1.80; figure 2). In eight studies, testosterone was associated with a significant rise in the frequency of satisfying sexual events compared with placebo or a comparator, irrespective of the mode of oestrogen delivery (mean difference 0.82, 95% CI 0.50 to 1.15; appendix p 8). In postmenopausal women, compared with placebo or a comparator, testosterone augmented sexual desire (standardised mean difference 0.36, 95% CI 0.22 to 0.50; $p<0.0001$; 95% prediction interval -0.12 to 0.84; figure 3), arousal (standardised mean difference 0.28, 95% CI 0.21 to 0.35; appendix p 11), orgasm (standardised mean difference 0.25, 95% CI 0.18 to 0.32; appendix p 12), pleasure (mean difference 6.86, 95% CI 5.19 to 8.52; appendix p 14), responsiveness (standardised mean difference 0.28, 95% CI 0.21 to 0.35;

appendix p 17), and self-image (mean difference 5.64, 95% CI 4.03 to 7.26; appendix p 18); moreover, testosterone reduced concerns (mean difference 8.99, 95% CI 6.90 to 11.08; appendix p 16). The three small studies that included premenopausal women showed no benefit over placebo or a comparator for the frequency of satisfying sexual events, total sexual function score, or any sexual function domain for which data were available (appendix pp 9, 10, 13, 15). Compared with placebo or a comparator, testosterone was associated with reduced personal sexual distress in all studies of postmenopausal women (standardised mean difference -0.27, 95% CI -0.36 to -0.17; appendix p 21). The one study that provided data for premenopausal women showed a reduction in personal sexual distress (mean difference -14.06, 95% CI -18.16 to -9.96; appendix p 22).

Pooled results of nine studies^{15,16,25,27,31,35,43,45,56} in 637 postmenopausal women showed that testosterone given

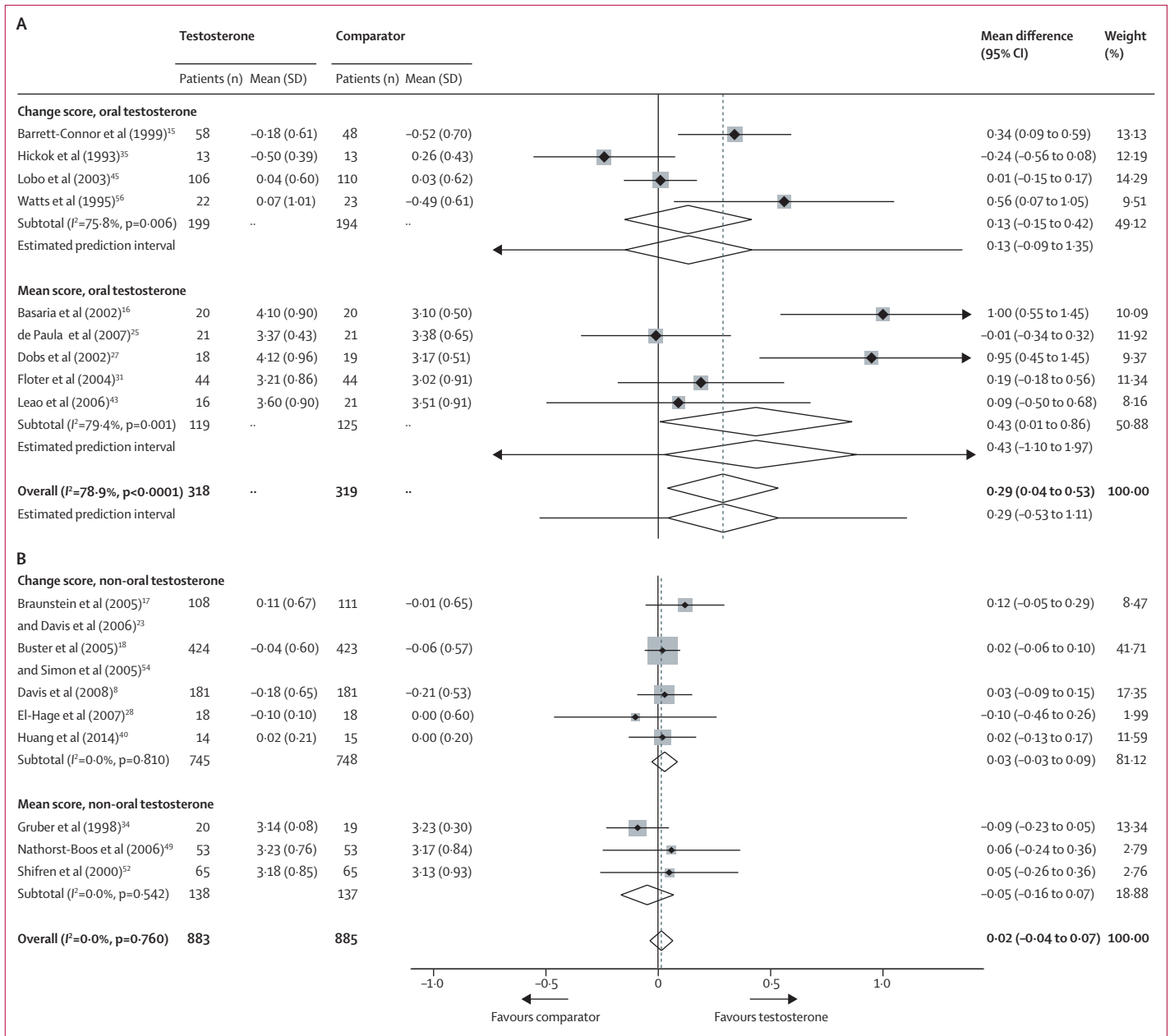


Figure 4: Effect of testosterone versus comparator on LDL-cholesterol for oral and non-oral testosterone
 Oral testosterone effects are shown in (A) and non-oral testosterone effects in (B). Studies reported outcomes in different ways such that they could not all be combined; some provided the change from baseline to end of study, others only provided the mean score for each treatment group at the end of the study. Data are mmol/L. Grey square indicates the weight of the study. Black diamond represents the mean difference per study and white diamond the mean difference overall. Horizontal lines depict the 95% CI. Vertical dotted line shows overall mean difference.

orally was associated with an increase in LDL-cholesterol (mean difference 0.29, 95% CI 0.04 to 0.53; $p<0.0001$; 95% prediction interval -0.53 to 1.11; figure 4A) and a reduction in total cholesterol (mean difference -0.32, 95% CI -0.50 to -0.14; appendix p 23) HDL-cholesterol (mean difference -0.40, 95% CI -0.49 to -0.30; appendix p 25), and triglycerides (mean difference -0.30, 95% CI -0.49 to -0.12; appendix p 27) compared

with placebo or a comparator. In ten studies^{8,17,18,23,28,34,38,49,52,54} of 1774 participants, testosterone administered non-orally was not associated with any significant lipid effects (mean difference 0.02, 95% CI -0.04 to 0.07; $p=0.76$; figure 4B; appendix pp 24, 26, 28). No effects of testosterone given both orally and non-orally were recorded for amounts of glucose and insulin in blood, blood pressure, or waist-to-hip ratio (appendix pp 29-31).

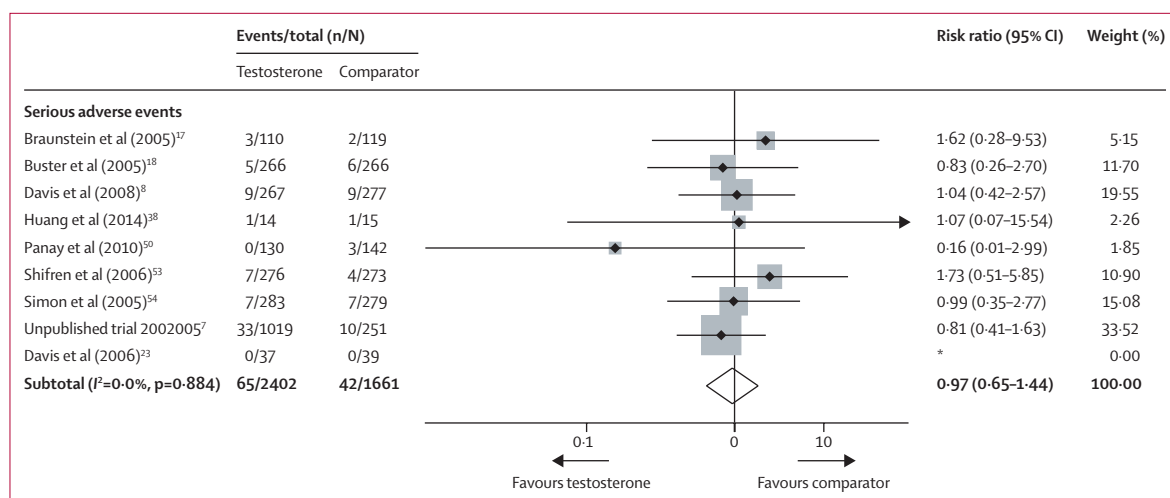


Figure 5: Effect of testosterone versus comparator on serious adverse events

Grey square indicates the weight of the study. Black diamond represents the risk ratio per study and white diamond the risk ratio overall. Horizontal lines depict the 95% CI. *Excluded.

Analysis of three studies^{25,34,43} in 118 participants that provided data for BMI showed no increase with testosterone (appendix p 32); however, analysis of data for weight from five studies^{18,34,43,54,58} in 2032 postmenopausal women indicated that testosterone led to weight gain (mean difference 0.48, 95% CI 0.16 to 0.79; appendix p 32).

Limited data were available for cognitive performance, from three studies of 159 postmenopausal women—two parallel group randomised controlled trials^{21,57} and one crossover study.⁴⁷ Data showed no effect of testosterone for any of the reported cognitive measures (appendix pp 33–35).

Together, data for 500 postmenopausal women from seven parallel group studies^{15,22,24,27,38,46,56} and one crossover study²⁹ showed no effect of testosterone on bone mineral density, body composition, or muscle strength (appendix pp 36–39).

Analysis of pooled data from four studies^{8,28,32,33}—two of 538 postmenopausal women and two of 67 premenopausal women—showed that testosterone treatment did not modify depressive mood, irrespective of menopausal status (appendix p 40). No benefits of testosterone were seen for psychological general wellbeing index scores from five studies^{8,21,23,38,52} in 810 postmenopausal women and three studies^{19,32,33} in 224 premenopausal women (appendix p 41).

Mammographic breast density did not change with testosterone treatment (data available for 345 postmenopausal women).^{7,20,37} One study⁷ of Ki67 staining of breast tissue—as an index of breast cell proliferation—did not show an effect of testosterone in 45 postmenopausal women. No other adverse breast health effects of testosterone were identified (breast pain, breast tenderness, breast engorgement, breast mass, or breast cancer; appendix pp 42, 43). Using data from one unpublished

study,⁵⁸ endometrial thickness did not increase with testosterone treatment in 843 postmenopausal women (appendix p 44).

Pooling data from 11 publications^{8,17–19,23,30,45,50,53,54,56} in 3264 participants showed that use of testosterone was associated with a greater likelihood of acne compared with placebo or a comparator (RR 1.46, 95% CI 1.11–1.92; appendix p 45). Data from 11 studies^{8,16–18,30,35,50,53,54,56} in 4178 participants showed that testosterone was associated with a greater likelihood of hair growth compared with placebo or a comparator (RR 1.69, 95% CI 1.33–2.14; appendix p 45). No other androgenic effects of testosterone (eg, alopecia, clitoromegaly, or voice change) were recorded compared with placebo or a comparator therapy (appendix p 45).

No serious adverse event was more frequent with testosterone compared with placebo or a comparator (RR 0.97, 95% CI 0.65–1.44; $p=0.884$; figure 5). Specifically, testosterone was not associated with more frequent reporting of cardiovascular events (eg, acute myocardial infarction, stroke, deep vein thrombosis, or cardiovascular deaths; appendix p 46). The overall proportion of patients who withdrew from treatment because of adverse events was similar across treatment groups (appendix p 47).^{8,17–19,23,50,53,54}

Among the 36 randomised controlled trials included in the meta-analysis, there was a high risk of attrition bias. Information about random sequence generation and allocation concealment was unclear in about half the trials. A summary of the proportion of trials that were at low, unclear, and high risk of bias for each domain is shown in figure 6. Details of the risk-of-bias assessment for included trials are provided in the appendix (p 48). A funnel plot could only be generated for sexual desire because of the few included studies reporting other outcomes; no small study effect was seen in the funnel plot (appendix p 49).

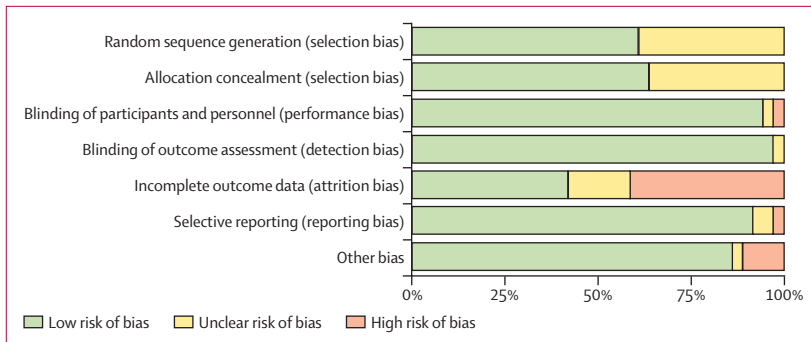


Figure 6: Review authors' assessments about risk-of-bias of included studies
Bars show percentages across all included studies.

Discussion

The findings of our systematic review and meta-analysis show beneficial treatment effects of testosterone for postmenopausal women on a comprehensive array of sexual function domains, the frequency of satisfying sexual events, and sexually associated personal distress. For premenopausal women, the only observed benefit was a reduction in sexually associated personal distress in one small study. Although testosterone treatment was associated with an increase in acne and hair growth, these adverse events have not led to participant withdrawal from clinical trials.⁸ Thus, mild androgenic effects might be a concern more to clinicians than to patients. Unfavourable cardiometabolic effects were restricted to adverse lipoprotein effects with oral testosterone.

The most frequently used female sexual function questionnaires are the Female Sexual Function Index (FSFI)⁵⁹ and the Profile of Female Sexual Function (PFSF).⁶⁰ Both provide assessments of desire, arousal, and orgasm, but only the PFSF, which was developed after the FSFI, assesses sexual concerns, responsiveness, and self-image. Diaries for satisfying sexual events and sexual distress scales have only been introduced in the past few years and, thus, none of the studies of oral testosterone provided data for these outcomes. Irrespective of the scales used and outcomes measured, consistent beneficial effects were seen with testosterone treatment for naturally and surgically menopausal women, whether or not they were also using oral or non-oral oestrogen concurrently. The clinical meaningfulness of these effects is much debated, with the relevance of one or two additional satisfying sexual events per month questioned. However, the beneficial effects of testosterone, as shown in our study, extend beyond a simple count of the number of satisfying sexual events per month. Sexually active postmenopausal women dissatisfied with sexual function report, on average, five sexual events per month.^{8,61} Increasing the number of occasions on which women experience a satisfying sexual encounter from never, or occasionally, to at least once or twice a month can strikingly improve the personal wellbeing and self-esteem of the affected women, their partners, and their

relationships.^{62,63} Further confirmation of the importance of these effects of testosterone is with the reduction in sexual concerns, improved sexual self-image, and diminished sexually associated distress reported in the present meta-analysis.

It is noteworthy that most of the studies we included in our systematic review and meta-analysis excluded women with identifiable causes of sexual concerns, such as dyspareunia, depression, or antidepressant use. Testosterone is not a first-line treatment for management of female sexual dysfunction and is only indicated after a full clinical assessment.⁶⁴ I^2 values for the pooled outcomes of satisfying sexual events (58%) and sexual desire (69%) indicated moderately high heterogeneity between the included studies. To estimate the potential effects of testosterone on these outcomes in future individual studies, prediction intervals were estimated. For both outcomes, the 95% prediction interval included zero meaning that, although the effect of testosterone for the completed studies was, on average, positive for satisfying sexual events and sexual desire, testosterone might not always be beneficial in an individual setting. For the other sexual outcomes, including sexual distress, the random-effects meta-analysis with 95% prediction intervals provided strong evidence that testosterone will be beneficial for postmenopausal women in future individual studies. This finding would suggest that the effects of testosterone on satisfying sexual events and sexual desire are more complex and affected by factors additional to the effects of testosterone on arousal, orgasm, and other measured outcomes.

The dearth of data pertaining to premenopausal women means no conclusions can be drawn about the efficacy of testosterone treatment for sexual dysfunction in this population. Larger studies in premenopausal women are needed to inform clinical recommendations.

Concern about the cardiometabolic safety of exogenous testosterone has been a barrier to approval of testosterone treatment for women. Findings of the present systematic review and meta-analysis show that oral testosterone adversely affects lipid profiles whereas non-oral treatment (eg, via transdermal patch or cream) has no such adverse effects. Although testosterone has been shown to be a vasodilator,⁶⁵ the overall effect on blood pressure was neutral. Overall, testosterone treatment was associated with a small but significant increase in weight, such that patients should be advised of this effect if testosterone treatment is being considered.

Although cognitive and musculoskeletal effects were included as primary outcomes, our study highlights the paucity of adequately powered clinical trials with data for these outcomes. For any conclusions to be made, standardisation of endpoints is needed for future studies, particularly for the assessment of cognitive performance and muscle health.

Claims have been made that testosterone treatment for women—even in supraphysiological doses—is

not masculinising.⁶⁶ Our analyses indicate testosterone treatment administered at doses intended to approximate physiological replacement to levels seen in premenopausal women is associated with a greater likelihood of acne and hair growth, but not alopecia, voice deepening, or cliteromegaly, compared with a comparator or placebo. Therefore, women who initiate testosterone treatment must be warned that these side-effects can occur and counselled against applying more than the prescribed dose. Anxiety, irritability, and depression are purported symptoms of testosterone insufficiency in women and testosterone treatment is suggested to be mood stabilising.⁶⁶ However, available data—although limited—do not support these conclusions. Without strong evidence of improvement in depressive symptoms and mood, testosterone should not be considered a treatment for depression in postmenopausal women. Our systematic review and meta-analysis indicates that current testosterone use was not associated with an increase in serious adverse events, including adverse endometrial and breast effects.

Our study has several strengths. First, we included data not only from studies identified by a comprehensive search of the published literature but also from completed but unpublished randomised controlled trials from the clinical development programme of the transdermal testosterone patch, identified from EMA and FDA submissions. Second, after contacting corresponding authors and accessing source data, we included several published studies previously excluded from reviews because of insufficient outcome data.^{3,67} These strengths make our study the most comprehensive systematic review and meta-analysis of testosterone treatment for women yet undertaken.

Our analysis has several limitations. First, a limitation of the included studies was attrition bias. In several studies, withdrawal and lost to follow-up was enhanced in women randomly allocated placebo compared with those assigned the active treatment. This bias is an issue for studies of several months' duration in which the main outcome is self-reported and the active treatment is effective. In the largest of the included studies,⁸ women randomly allocated placebo were more likely to discontinue because of a lack of benefit, resulting in participants who persisted possibly being more likely to be placebo responders. A second limitation was that not all studies that reported sexual function outcomes recruited women with sexual dysfunction, and among those that had sexual dysfunction as an inclusion criterion, the definition of sexual dysfunction was not consistent. Third, we were unable to include the outcomes of two large double-blind randomised controlled trials of a transdermal testosterone gel, in which a therapeutic effect of testosterone on satisfying sexual events was not detected, because the findings have only been reported in abstract form, with insufficient numerical and methodological data to enable inclusion.^{68,69} Not only were the overall increases in

satisfying sexual events per month in these two studies greater than seen across the transdermal testosterone patch studies, but the placebo groups in these two trials had increases in satisfying sexual events three fold to fourfold greater than seen with placebo in other testosterone patch studies.^{8,50,53} This finding suggests there could have been some fundamental differences in either the study populations or the conduct of these studies, compared with other published studies. Finally, the reporting of outcomes for premenopausal women was limited by the paucity of studies. Similarly, findings for several of our a priori outcomes—notably, effects on musculoskeletal health, cognitive performance, mood and wellbeing, breast cancer risk, and cardiovascular disease—are inconclusive. This drawback is attributable to scant published data (these being mostly secondary outcomes for which data were available and analyses underpowered) and use of different outcome measures.⁶⁵

Our comprehensive systematic review provides robust support for a trial of testosterone treatment, using a dose appropriate for women, when clinically indicated in postmenopausal women.⁶⁴ The absence of any approved testosterone formulations for women in any country, however, is a major treatment barrier. This shortfall urgently needs to be addressed to eradicate the widespread practice of women being treated with male formulations and compounded products, resulting in testosterone concentrations several fold greater than appropriate for women. Further research is needed to clarify the effects of testosterone treatment in premenopausal women and the effects on musculoskeletal and cognitive health and long-term safety.

Contributors

RMI, RJB, and SRD contributed to study design and preparation of the figures. RMI contributed to the literature search and data extraction. RMI, RJB, SG, and SRD contributed to study selection. RMI, RJB, and MJP contributed to the risk-of-bias analysis and data analysis. All authors contributed to data interpretation and review of the report. RMI and SRD contributed to writing of the report.

Declaration of interests

SRD declares honoraria from Besins Healthcare and Pfizer Australia and has been a consultant to Besins Healthcare, Mayne Pharmaceuticals, Lawley Pharmaceuticals, and Que Oncology. RMI, RJB, SG, and MJP declare no competing interests.

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Sexual Dysfunction in Women: A Practical Approach

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Sexual dysfunction in women is a common and often distressing problem that has a negative impact on quality of life and medication compliance. The problem is often multifactorial, necessitating a multidisciplinary evaluation and treatment approach that addresses biological, psychological, sociocultural, and relational factors. Criteria for sexual interest/arousal disorder require the presence of at least three specific symptoms lasting for at least six months. Life-long anorgasmia may suggest the patient is unfamiliar or uncomfortable with self-stimulation or sexual communication with her partner. Delayed or less intense orgasms may be a natural process of aging due to decreased genital blood flow and dulled genital sensations. Genito-pelvic pain/penetration disorder includes fear or anxiety, marked tightening or tensing of the abdominal and pelvic muscles, or actual pain associated with attempts toward vaginal penetration that is persistent or recurrent for at least six months. Treatment depends on the etiology. Estrogen is effective for the treatment of dyspareunia associated with genitourinary syndrome of menopause. Testosterone, with and without concomitant use of estrogen, is associated with improvements in sexual functioning in naturally and surgically menopausal women, although data on long-term risks and benefits are lacking. Bupropion has been shown to improve the adverse sexual effects associated with antidepressant use; however, data are limited. Psychotherapy or sex therapy is useful for management of the psychological, relational, and sociocultural factors impacting a woman's sexual function. Clinicians can address many of these issues in addition to providing education and validating women's sexual health concerns. (*Am Fam Physician*. 2015;92(4):281-288. Copyright © 2015 American Academy of Family Physicians.)



The online version of this article includes supplemental content at <http://www.aafp.org/afp>.

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► Patient information: A handout on this topic is available at <http://familydoctor.org/familydoctor/en/diseases-conditions/sexual-dysfunction-women.html>.

Female sexual dysfunction is a general term comprising several sexual health concerns that can be distressing for patients, including female sexual interest/arousal disorder, female orgasmic disorder, and genito-pelvic pain/penetration disorder. These sexual health concerns are not considered dysfunctions unless they cause distress. About 12% of women in the United States report distressing sexual health concerns, although as many as 40% report sexual concerns overall.¹

Etiology and Pathophysiology

The etiology of female sexual dysfunction is multifactorial, encompassing biological, psychological, relational, and sociocultural factors.² Biological factors may impact sexual function in a variety of ways. Some chronic illnesses, such as vascular disease, diabetes mellitus, neurologic disease, and malignancy, can directly or indirectly impact sexual function (*Table 1*).^{3,4} Aging itself is associated with decreased sexual responsiveness, sexual activity, and libido.^{4,5}

Hormonal changes occurring in midlife may impact a woman's sexual function. Menopause is marked by a decline in ovarian hormone levels, which occurs gradually in natural menopause but may be sudden if menopause occurs because of surgery, radiation, or chemotherapy. Decreased vaginal lubrication and dyspareunia are associated with low estradiol levels; however, the association between low sexual desire and lower estradiol levels has been inconsistent. Testosterone levels do not correlate with female sexual function or overall well-being, possibly because of the difficulty in accurately measuring free and total testosterone levels at the lower end of the female range.⁴ Although androgens are positively associated with improvements in all aspects of sexual functioning (e.g., subjective arousal, vaginal blood flow, sexual desire, orgasm), there is no lower level of testosterone that predicts sexual dysfunction, and androgen levels are not used to define an androgen deficiency syndrome in women.

Sexual Dysfunction in Women

Table 1. Medical Conditions That Potentially Impact Sexual Function

Condition	Type of dysfunction				Comments
	Desire	Arousal	Orgasm	Pain	
Arthritis				+	Decreased mobility and chronic pain may impair sexual function
Coronary artery disease		+			—
Dermatologic conditions (e.g., vulvar lichen sclerosus, vulvar eczema, psoriasis)				+	—
Diabetes mellitus	+				—
Gynecologic conditions (e.g., sexually transmitted infections, endometriosis, chronic pelvic pain, pelvic pain following childbirth, pelvic organ prolapse)				+	—
Hypertension	+				Impact of hypertension or treatment is unclear; one study found an association with low desire
Hypothyroidism		+	+		Increased problems with lubrication and orgasm
Malignancy and treatment (e.g., breast, anal, colorectal, bladder, and gynecologic cancers)	+	+	+	+	Sexual function may be directly or indirectly impacted by cancer diagnosis and treatment; factors include cancer diagnosis, disease itself, treatment (surgery, radiation, chemotherapy), and body image
Neuromuscular disorders, spinal cord injury, multiple sclerosis	+	+	+	+	Direct impact on sexual response; indirect effect on desire may be mediated by arousal disorders or pain
Parkinson disease, dementia, head injury	+				Desire may be increased or decreased
Pituitary tumor, hyperprolactinemia	+				—
Renal failure					Dialysis is associated with sexual dysfunction; no data on which type of sexual dysfunction is affected
Urinary incontinence	+	+		+	—

Information from references 3 and 4.

Serotonin-enhancing medications have an inhibitory effect on sexual function. Sexual dysfunction induced by selective serotonin reuptake inhibitor use is common, with an incidence between 30% and 70%, and may include difficulty with sexual desire, arousal, and orgasm.⁴ Further, many other commonly prescribed medications may adversely affect sexual functioning,

including antiestrogens, such as tamoxifen and aromatase inhibitors, and oral estrogens, including combined hormonal contraception (*Table 2*).⁶

The most common psychological factors impacting female sexual function are depression, anxiety, distraction, negative body image, sexual abuse, and emotional neglect. Common contextual or sociocultural factors

that cause or maintain sexual dysfunction include relationship discord, partner sexual dysfunction (e.g., erectile dysfunction), life stage stressors (e.g., transition into retirement, children leaving home), and cultural or religious messages that inhibit sexuality.⁷

Evaluation

Assessment of female sexual dysfunction is best approached using a biopsychosocial model (eFigure A), and should include a sexual history and physical examination. Laboratory testing is usually not needed to identify causes of sexual dysfunction.⁸ Table 3 includes important questions to ask patients during a sexual functioning assessment.⁸

FEMALE SEXUAL INTEREST/AROUSAL DISORDER

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-5), combines hypoactive sexual desire disorder and female sexual arousal disorder into a single disorder: female sexual interest/arousal disorder.⁹ Whereas sexual desire is the motivation to have sex, sexual arousal refers to the physiologic processes of arousal, including vaginal lubrication and genital warmth related to blood flow. Women commonly report experiencing these as part of the same process.¹⁰ The DSM-5 criteria for female sexual interest/arousal disorder are presented in Table 4.⁹

It is important to determine whether the patient's problem with desire or arousal is a dysfunction or a normal variation of sexual response. The following examples are not considered sexual dysfunction: a patient reports little or no spontaneous desire but continues to experience responsive desire; a patient maintains spontaneous or responsive desire but reports a desire discrepancy between herself and her partner; a patient has reduced physiologic sexual arousal (e.g., decreased vaginal lubrication or genital blood flow) related to menopausal transition.

FEMALE ORGASMIC DISORDER

DSM-5 criteria for female orgasmic disorder include a marked delay in orgasm, infrequency or absence of orgasm, or less intense orgasm for at least six months in 75% to

Table 2. Medications Associated with Female Sexual Dysfunction

Medication	Type of dysfunction		
	Desire disorder	Arousal disorders	Orgasm disorders
Amphetamines and related anorectic medications			+
Anticholinergics		+	
Antihistamines		+	
Cardiovascular and antihypertensive medications			
Antilipids	+		
Beta blockers	+		
Clonidine	+	+	
Digoxin	+		+
Methyldopa	+		
Spironolactone	+		
Hormonal preparations			
Antiandrogens	+	+	+
Danazol	+		
Gonadotropin-releasing hormone agonists	+		
Gonadotropin-releasing hormone analogues	+	+	
Hormonal contraceptives	+		
Tamoxifen	+	+	
Ultra-low-potency contraceptives	+	+	
Monoamine oxidase inhibitors			
Trazodone	+		
Venlafaxine	+		
Narcotics			+
Psychotropics			
Antipsychotics	+		+
Barbiturates	+	+	+
Benzodiazepines	+	+	
Lithium	+	+	+
Selective serotonin reuptake inhibitors	+	+	+
Tricyclic antidepressants	+	+	+
Other			
Aromatase inhibitors	+	+	
Chemotherapeutic agents	+	+	
Histamine H ₂ blockers and promotility agents	+		
Indomethacin	+		
Ketoconazole	+		
Phenytoin (Dilantin)	+		

Information from reference 6.

Table 3. Questions to Facilitate the Assessment of Female Sexual Functioning

Question	Interpretation of "Yes" answers*
Are you currently sexually active (with men, women, or both)?	Continue to the next question (if "No," also continue to the next question)
Do you have any sexual health concerns?	Continue to the next question
Specifically, any distress related to:	
Your level of sexual desire/interest?	Assess for sexual interest/arousal disorder
Your ability to become or stay sexually aroused ("turned on," vaginal lubrication, blood flow/warmth/tingly feelings in genitals)?	Assess for sexual interest/arousal disorder
Your ability to experience or reach the desired intensity of an orgasm?	Assess for orgasmic disorder
Are you experiencing any genital pain?	Assess for genito-pelvic pain/penetration disorder, genitourinary syndrome of menopause, and pelvic floor muscle dysfunction
Vaginal dryness or burning?	Assess for genitourinary syndrome of menopause
Pain with sexual activity (insertional or deeper pain)?	Assess for genitourinary syndrome of menopause and pelvic floor muscle dysfunction

*—Starting with the second question, if the answer is "No," the assessment can end.
Information from reference 8.

100% of sexual interactions.⁹ Establishing the presence of orgasm is important, because many women may not know whether they have experienced orgasm.¹¹ The next step is determining whether these problems are causing distress. About one-half of women who do not consistently reach orgasm during sexual activity do not report distress.¹ If distress exists, the assessment follows the biopsychosocial model with the addition of several key questions that will assist in treatment planning: Is this a change in previous orgasmic functioning? Does this difficulty occur during self-stimulation, partnered sexual activity, or both? Does this difficulty occur across different sexual activities (e.g., oral, manual, vaginal penetration) and with different sex partners?

Orgasmic difficulties may be lifelong (present since sexual debut) or acquired (starting after a period of no dysfunction). Lifelong anorgasmia may suggest the patient is unfamiliar or uncomfortable with self-stimulation or sexual communication with her partner, or lacks adequate sex education.¹² Delayed or less intense orgasms may be related to decreased genital blood flow and dulled genital sensations occurring naturally with aging. These examples are not considered sexual dysfunction.

The clinician should determine whether orgasmic difficulties occur only with certain types of stimulation,

situations, or partners. If the patient reports difficulty during partnered sexual activity but not with self-stimulation, it may be the result of inadequate sexual stimulation.¹¹ Biological factors requiring assessment and treatment include medical conditions and use of medications that impact sexual functioning¹¹ (Tables 1^{3,4} and 2⁶).

GENITO-PELVIC PAIN/PENETRATION DISORDER

In the DSM-5, vaginismus and dyspareunia are combined in genito-pelvic pain/penetration disorder. This disorder of sexual pain is defined as fear or anxiety, marked tightening or tensing of the abdominal and pelvic muscles, or actual pain with vaginal penetration that is persistent or recurrent for at least six months. This may be lifelong or acquired after a period of no dysfunction.⁹ The clinician should determine if the pain occurs with initial vaginal penetration, deeper penetration, or both.

Treatment

Although female sexual dysfunction often requires multidisciplinary treatment, even the initial visit can be beneficial. Table 5 summarizes the PLISSIT (permission, limited information, specific suggestions, intensive therapy) model for addressing sexual health with patients.¹³

The unique predisposing, precipitating, and maintaining factors for a woman's sexual dysfunction will determine the treatment plan.^{7,14} Biological factors, such as medication use, are best treated by the clinician.¹⁵ Strategies for managing antidepressant-induced dysfunction include reducing the dose if possible, switching to an antidepressant with fewer sexual adverse effects

(vs. proactively initiating an antidepressant with fewer sexual adverse effects), or adding bupropion (Wellbutrin) as an adjunct.¹⁶ A Cochrane review supports the addition of bupropion in higher dosages (150 mg twice daily) for treatment of antidepressant-induced sexual dysfunction in women, but additional study is needed.¹⁷ In one small study, the addition of sildenafil (Viagra) reduced sexual dysfunction induced by selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors.¹⁸

Female genital sexual pain disorders are complex and most effectively managed with a comprehensive, multidisciplinary approach that addresses contributing biopsychosocial factors.¹⁹ Sexual pain with deeper vaginal penetration suggests the possibility of a musculoskeletal component. This pain may be described as a deeper pelvic pain associated with penetrative sexual activity, pain that radiates to the low back or inner thigh, or pain that persists for some time after vaginal penetration.²⁰ Pelvic floor dysfunction is optimally treated by a physical therapist trained in treating this condition. Consistent painless sexual activity and sexual stimulation with the therapeutic use of a vibrator may also help maintain vaginal health.²¹ If a patient reports painful sexual activity, it is important to advise her to stop engaging in this activity because it can increase situational anxiety, resulting in tensing of the pelvic floor muscles and increasing pain. Psychotherapy or sex therapy is useful for women who have relational or sociocultural factors contributing to their pain, and for those who experience anxiety in conjunction with their pain.^{22,23} Psychological, interpersonal, and sociocultural factors are most appropriately treated by a mental health subspecialist. Sexual pain during initial vaginal penetration may suggest inadequate sexual arousal before penetration, genitourinary syndrome of menopause (formerly termed vulvovaginal atrophy),²⁴ or provoked vestibulodynia.

Group cognitive behavior therapy may be effective for low sexual desire.⁸ Mindfulness-based interventions have been shown to effectively treat several types of female sexual dysfunction, including low sexual desire and arousal, and acquired anorgasmia.^{7,25,26}

Table 4. DSM-5 Criteria for Female Sexual Interest/Arousal Disorder

- A. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following:
1. Absent/reduced interest in sexual activity.
 2. Absent/reduced sexual/erotic thoughts or fantasies.
 3. No/reduced initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate.
 4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).
 5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual).
 6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).
- B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.
- C. The symptoms in Criterion A cause clinically significant distress in the individual.
- D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify whether:

Generalized: Not limited to certain types of stimulation, situations, or partners.

Situational: Only occurs with certain types of stimulation, situations, or partners.

Specify current severity

Mild: Evidence of mild distress over the symptoms in Criterion A.

Moderate: Evidence of moderate distress over the symptoms in Criterion A.

Severe: Evidence of severe or extreme distress over the symptoms in Criterion A.

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Table 5. PLISSIT Model for Addressing Sexual Health with Women

Steps	Examples of what to say to patients
Permission: Give patient permission to speak about her sexual health and to do what she is already doing sexually (or may want to do).	"This is important. Thank you for sharing. Many postmenopausal women report a decrease in sexual desire."
Limited information: Provide basic accurate sex education (e.g., female sexual response cycle, impact of aging on sexual function, anatomy).	"Sexual desire changes with age. After menopause you may experience more responsive desire than spontaneous desire."
Specific suggestions: Provide simple suggestions to increase sexual function (e.g., lubricant use, vibrator use, ways to increase emotional intimacy).	"Your responsive sexual desire may benefit from being more playful with sexual activity. Talk with your partner about how to be more intentional sexually."
Intensive therapy: Validate the patient's concerns and refer her to a subspecialist (see eTable A for resources).	"Your sexual health is important. I'd like to refer you to someone with expertise in sexual health."

Information from reference 13.

Directed masturbation training is the treatment of choice for lifelong anorgasmia.²⁷⁻²⁹ eTable A includes resources for referral and further information on sexual health.

Special Considerations

MENOPAUSE

Sexual health concerns are common in natural or surgically induced menopause, particularly sexual pain related to genitourinary syndrome of menopause. A Cochrane review showed that hormone therapy (estrogen alone or in combination with a progestogen) was associated with a small to moderate improvement in sexual function, especially pain, in symptomatic or early menopausal women.³⁰ Estrogen treatment is highly effective for genitourinary syndrome of menopause and related dyspareunia; local vaginal estrogen is preferred if vaginal dryness is the primary concern.^{14,21,31} Ospemifene (Osphena) is a selective estrogen receptor modulator that has been shown to improve the vaginal maturation index, vaginal pH, and symptoms of vaginal dryness.^{21,32,33} The U.S. Food and Drug Administration (FDA) has approved it for treatment of moderate to severe dyspareunia. The route of administration of estrogen can impact sexual function. Oral estrogens increase sex hormone-binding globulin, which reduces available free testosterone and may thereby adversely impact sexual function, whereas transdermal estrogens have no such effect.⁶

Women with genitourinary syndrome of menopause and sexual pain may have dysfunctional pelvic floor muscles, which may become tense or tight as a result of

ongoing vaginal dryness and discomfort or pain with sexual activity.³⁴ Pelvic floor physical therapy may benefit these women.³⁴

Randomized controlled trials involving naturally or surgically menopausal women with low sexual desire or arousal have shown improvements in sexual function with transdermal testosterone therapy (with or without concomitant estrogen therapy).³⁵⁻³⁹ However, overall, data on the benefit of testosterone therapy are limited and inconsistent.^{35,40,41} The Endocrine Society suggests considering a three- to six-month trial of testosterone therapy for postmenopausal women with low sexual desire associated with distress. However, because of the lack of long-term data on safety and effectiveness, it does not recommend routine testosterone treatment for women with low androgen levels related to hypopituitarism, bilateral oophorectomy, or adrenal insufficiency.⁴¹ Testosterone therapy is not FDA-approved for use in women, and using testosterone formulations made for men is discouraged. If therapy is initiated, clinical evaluation and laboratory monitoring of testosterone levels are suggested to evaluate for overuse and signs of hyperandrogenism (e.g., acne, hair growth).⁴¹

SEXUAL DISTRESS WITHOUT DYSFUNCTION

If a patient reports distress but does not meet criteria for sexual dysfunction, intervention is still needed. Women who report low desire or arousal, difficulty with orgasm, or inadequate sexual stimulation may benefit from normalization, sexual health education, and referral to a sex therapist.⁴²

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Bupropion (Wellbutrin) in higher dosages (150 mg twice daily) has been shown to be effective as an adjunct for antidepressant-induced sexual dysfunction in women.	B	17
Sildenafil (Viagra) may benefit women with sexual dysfunction induced by selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor use.	B	18
Female genital sexual pain disorders are complex and most effectively managed with a comprehensive, multidisciplinary approach that addresses contributing biopsychosocial factors.	C	19
Group cognitive behavior therapy has been shown to effectively treat low sexual desire.	C	7
Mindfulness-based interventions have been shown to effectively treat low sexual desire and arousal, and acquired anorgasmia.	B	7, 25, 26
Directed masturbation is recommended for lifelong anorgasmia.	C	27-29
Local vaginal estrogen therapy is recommended and preferred over systemic estrogen therapy for treatment of genitourinary syndrome of menopause and related dyspareunia when vaginal dryness is the primary concern. Because of potential adverse effects, the use of estrogens, especially systemic estrogens, should be limited to the shortest duration compatible with treatment goals.	A	14, 21, 31
Ospemifene (Osphena) is modestly effective for treatment of dyspareunia.	B	21, 32, 33
Transdermal testosterone, with or without concomitant estrogen therapy, has been shown to be effective for short-term treatment of low sexual desire or arousal in natural and surgically induced menopause.	B	35, 36

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

The female sexual response cycle (*eFigure B*) is an important educational tool that clinicians can use when counseling women with sexual concerns. Women enter this cycle of sexual response with spontaneous sexual drive (i.e., the internal desire for sexual activity) or more commonly from a nonsexual state. A woman in a nonsexual state may engage in a sexual encounter for a number of nonsexual reasons (e.g., to please her partner, to feel emotionally connected, out of a sense of duty). Once sexual activity (with adequate stimulation) begins, the woman may experience sexual arousal, which may lead to responsive sexual desire and motivation for future sexual responsiveness.⁴² This model delineates spontaneous and responsive desire, normalizes the sexual experience of arousal preceding desire, and stresses emotional intimacy as a major motivator for sexual responsiveness.

Data Sources: A comprehensive English-language search of several databases from 2004 to August 7, 2014, was conducted and included MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, PsycINFO, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, U.S. Preventive Services Task Force recommendations, National Guideline Clearinghouse, Agency for Healthcare Research and Quality evidence reports, the Institute for Clinical Systems Improvement guidelines, and Essential Evidence. Keywords included dyspareunia, libido, orgasm, orgasmic, orgasms, sexual arousal, sexual desire, and sexual dysfunction. Search dates: August to October 2014.

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eTable A. Resources for More Information on Female Sexual Health and Referral

Resources for clinicians

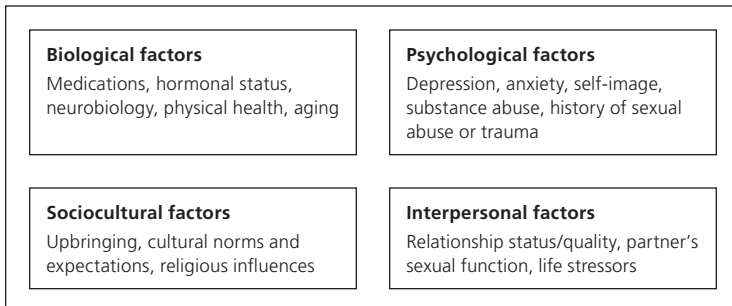
- American Association of Sexuality Educators, Counselors, and Therapists
<http://www.aamft.org>
- International Society for the Study of Women’s Sexual Health
<http://www.isswsh.org>
- Society for Sex Therapy and Research
<http://www.sstarnet.org>

Couples therapy

- American Association for Marriage and Family Therapy
<http://www.aamft.org>

Pelvic physical therapy

- American Physical Therapy Association
http://www.moveforwardpt.com/symptomsconditionsdetail.aspx?cid=4c28867f-b11f-4148-a21c-f8b6c5ac7002#.VP0NO_mjOm4
- International Pelvic Pain Society
<http://www.pelvicpain.org>



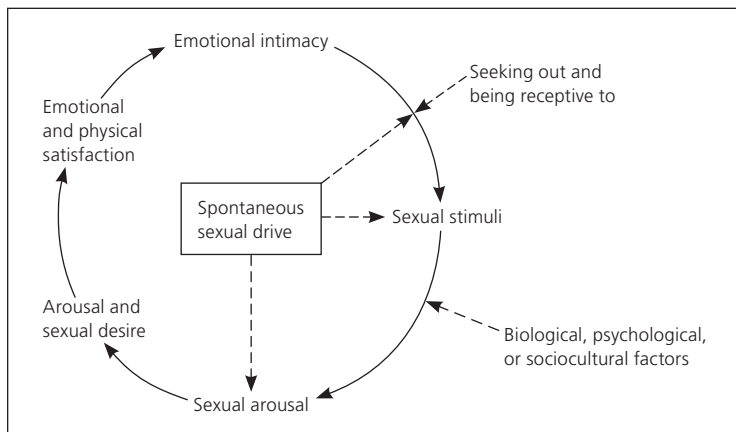
eFigure A. Biopsychosocial model of female sexual dysfunction. Various factors from different realms can promote or hinder normal sexual function.

Information from:

Bitzer J, Giraldi A, Pfaus J. Sexual desire and hypoactive sexual desire disorder in women. Introduction and overview. Standard operating procedure (SOP Part 1). *J Sex Med.* 2013;10(1):36-49.

Fugl-Meyer KS, Bohm-Starke N, Damsted Petersen C, Fugl-Meyer A, Parish S, Giraldi A. Standard operating procedures for female genital sexual pain. *J Sex Med.* 2013;10(1):83-93.

Latif EZ, Diamond MP. Arriving at the diagnosis of female sexual dysfunction. *Fertil Steril.* 2013;100(4):898-904.



eFigure B. Female sexual response cycle. Interrelated factors work together to promote sexual response.

Adapted with permission from Basson R. Human sex-response cycles. J Sex Marital Ther. 2001;27(1):34.



The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women

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Abstract

The International Society for the Study of Women's Sexual Health process of care (POC) for management of hypoactive sexual desire disorder (HSDD) algorithm was developed to provide evidence-based guidelines for diagnosis and treatment of HSDD in women by health care professionals. Affecting 10% of adult females, HSDD is associated with negative emotional and psychological states and medical conditions including depression. The algorithm was developed using a modified Delphi method to reach consensus among the 17 international panelists representing multiple disciplines. The POC starts with the health care professional asking about sexual concerns, focusing on issues related to low sexual desire/interest. Diagnosis includes distinguishing between generalized acquired HSDD and other forms of low sexual interest. Biopsychosocial assessment of potentially modifiable factors facilitates initiation of treatment with education, modification of potentially modifiable factors, and, if needed, additional therapeutic intervention: sex therapy, central nervous system agents, and hormonal therapy, guided in part by menopausal status. Sex therapy includes behavior therapy, cognitive behavior therapy, and mindfulness. The only central nervous system agent currently approved by the US Food and Drug Administration (FDA) for HSDD is flibanserin in premenopausal women; use of flibanserin in postmenopausal women with HSDD is supported by data but is not FDA approved. Hormonal therapy includes off-label use of testosterone in postmenopausal women with HSDD, which is supported by data but not FDA approved. The POC incorporates monitoring the progress of therapy. In conclusion, the International Society for the Study of Women's Sexual Health POC for the management of women with HSDD provides a rational, evidence-based guideline for health care professionals to manage patients with appropriate assessments and individualized treatments.

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The International Society for the Study of Women's Sexual Health (ISSWSH) process of care (POC) for hypoactive sexual desire disorder (HSDD) in women provides a consensus management guideline for the diagnosis and treatment of HSDD, the most common sexual dysfunction in women (Figure 1). Given recent research and increasing public awareness about HSDD, greater

numbers of women are anticipated to seek treatment for HSDD from a health care professional (HCP). This POC model consists of an evidence-based approach to identification, diagnosis, and treatment, emphasizing biopsychosocial assessment and education. It highlights opportunities to address modifiable factors, includes patient needs and preferences in the decision-making process, and defines



For editorial comment, 406; for related articles, see pages 429 and 458

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ARTICLE HIGHLIGHTS

- Hypoactive sexual desire disorder (HSDD), the most common sexual dysfunction in women, has been associated with negative emotional and psychological states, as well as medical conditions including depression; therefore, a guideline for management of HSDD has been developed for health care professionals by the International Society for the Study of Women's Sexual Health.
- This guideline starts with questions to ask regarding sexual health concerns and moves on to diagnosis of generalized acquired HSDD. Treatment begins with education, modification of potentially modifiable factors, and, if needed, additional therapeutic interventions.
- The choice of therapeutic intervention is most often dependent on patient (and partner) preferences and goals.

situations for specialized referral. The model incorporates the following essential principles: (1) identification of subtypes of HSDD, (eg, generalized vs situational and acquired vs lifelong), with emphasis on associated concomitant medical and psychological factors, (2) importance of patient and partner education during all phases of management, (3) goal-oriented focus with patient and partner needs and preferences guiding recommendations for treatment, and (4) clear guidance for follow-up and consideration for referral.

METHODS

This HSDD POC was developed under the auspices of the ISSWSH with input from an international multidisciplinary panel. After a planning conference call, panelists were asked to individually conduct an evidence-based literature review. The panel of 17 researchers and clinicians, ISSWSH members and non-members, convened for 2 days to review and discuss management strategies for HSDD using a modified Delphi method.¹⁻³ This iterative process involved presentations summarizing the current literature, debate and discussion of divergent opinions concerning HSDD assessment and management, and consensus development of a clinical guideline for the HCP. There was no industry participation in any part of the process.

BACKGROUND

Definition of HSDD

Women who are persistently and recurrently not interested in sexual activity who report the absence of sexual fantasies and who are bothered by their lack of sexual interest are said to be experiencing distressing low sexual desire.⁴ Because there is substantial experimental and clinical evidence for this classification,⁴⁻⁸ we will adopt the widely utilized diagnostic label of HSDD to describe women who are distressed by their clinically low levels of sexual desire and utilize the definition developed by the ISSWSH nomenclature committee.⁹ This definition states:

HSDD manifests as *any* of the following for a minimum of 6 months:

- Lack of motivation for sexual activity as manifested by:
 - Decreased or absent spontaneous desire (sexual thoughts or fantasies); or
 - Decreased or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity;
- Loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders;
- And is combined with clinically significant personal distress that includes frustration, grief, guilt, incompetence, loss, sadness, sorrow, or worry.

Hypoactive sexual desire disorder may be lifelong or acquired and generalized or situational. This definition should be understood in a biopsychosocial context and therefore can be applied to both somatic and psychiatric diagnostic schema.⁹

Clinical Significance and Epidemiology

Hypoactive sexual desire disorder is associated with negative emotional and psychological states, as well as medical conditions including depression.¹⁰⁻¹² Women with HSDD may experience decreased quality of life including impaired body image, self-confidence, and self-worth and feel less connected to their partners.¹⁰ Women with HSDD also have increased health care costs and health burden.^{13,14}

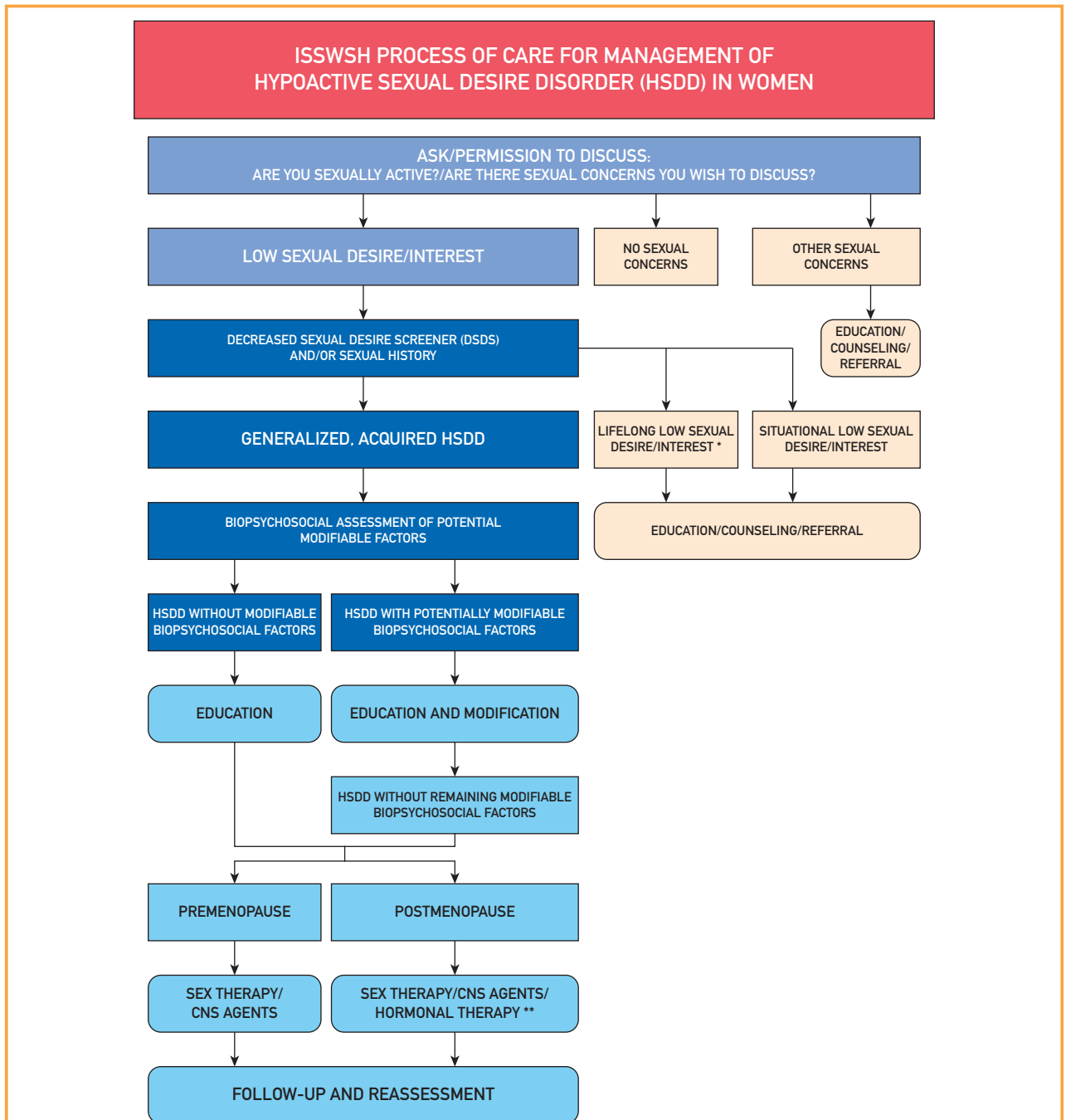


FIGURE 1. The International Society for the Study of Women's Sexual Health (ISSWSH) process of care for hypoactive sexual desire disorder (HSDD) algorithm begins with asking or having permission to discuss sexual concerns and focuses specifically on women who have concerns with their low sexual desire/interest. Initiation of diagnosis starts with the Decreased Sexual Desire Screener or a sexual history. Women with other sexual dysfunctions or those with lifelong or situational low sexual desire/interest are not specifically addressed in this algorithm. Women with generalized acquired HSDD then undergo a focused medical assessment to identify potentially modifiable biopsychosocial factors. Therapeutic intervention begins with education/modification of recognized modifiable factors. Women whose HSDD persists are categorized by menopausal status, and appropriate therapeutic interventions are then followed/reassessed. CNS = central nervous system. *Women with lifelong low sexual desire/interest without distress/bother may characterize themselves as asexual and should not be considered for treatment. **Women in the late reproductive years.

Epidemiologic studies assessing the prevalence of HSDD in women vary according to the (1) definition (low desire/interest; HSDD), (2) group of participants (general population, medical presentation, sex therapy clinics, age group, menopausal status, nationality), and (3) methodology (eg, self-report, interview, questionnaire; face-to-face or online; single-question response, completion of validated scale; inclusion of distress in the definition). These differences in study design have produced prevalence estimates ranging from 17% to over 50%.¹⁵⁻²⁰

In the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study, a widely cited, large population-based survey of 50,001 US women (completers, 31,531; 63% response rate; aged 18-102 years), low desire was the most common sexual problem, reported in 37.7% of participants; low desire with distress (HSDD) was present in approximately 10% of women and was more common than distressing arousal or orgasm difficulties.²¹

Physiology

Sexual desire is regulated by key regions in the brain through the action of various neurotransmitters.²²⁻²⁴ Dopamine, melanocortin, oxytocin, vasopressin, and norepinephrine mediate sexual excitation, whereas opioid, serotonin, endocannabinoid, and prolactin systems mediate sexual inhibition.^{22,23} Although the underlying biological causes of HSDD remain unknown, generalized HSDD likely involves either a predisposition toward inhibitory processes or neuroadaptations that result in decreased excitation, increased inhibition, or a mixture of the two.^{6,25,26} Alterations in brain function and structure may be additionally modulated or reinforced by experience and behavior (experience-based neuroplasticity), further propagating the condition. This perspective is consistent with differential brain activity patterns and structural differences between women with and without HSDD.²⁷⁻³⁰

SCREENING FOR SEXUAL PROBLEMS

The optimal strategy for detecting sexual problems (desire, arousal, orgasm, pain) is “simply to ask” (Figure 1) during the patient visit. The

sexual health interview should be conducted when it feels most natural in the encounter. Begin by asking, “Are you sexually active?” Whether the patient answers “yes” or “no,” continue by asking a direct screening question such as, “Are there sexual concerns you wish to discuss?”⁵ Explain that sexual problems are common and facilitate screening by assuring the patient that you, the physician, are comfortable discussing sexual issues. To normalize and legitimize sexual concerns, you may introduce a direct screening question with a “ubiquity statement” such as, “Many women having [the characteristics of the patient] have concerns about sexual functioning; what about you?”³¹

The start of ubiquity statements may include medical, social, and life-cycle issues such as, “Many women with diabetes...” or “Many women going through menopause...” You may follow the ubiquity statement with an open-ended invitation such as, “Tell me about it.” If a woman reports low desire, it is important to assess the presence of distress related to low desire, which is integral to the definition of HSDD.⁹ If HSDD is present, this POC should be followed. If her sexual problem is arousal, orgasm, or pain, other clinical evaluations and interventions such as education, counseling, or referral should be considered.

DIAGNOSIS

Recommended diagnostic strategies include use of the Decreased Sexual Desire Screener (DSDS) and/or a sexual history to determine the type of HSDD.

Decreased Sexual Desire Screener

The DSDS is a validated instrument for confirming the diagnosis of generalized acquired HSDD in women [*level of evidence (LoE) 2*].^{32,33} The DSDS is brief, effective, user-friendly, and self-completed and requires no special training to administer/interpret (Figure 2).^{34,35} The DSDS serves to grant permission and encourage dialogue for screening for HSDD and identification of etiologic factors, obviating potential patient and physician embarrassment.

The screener includes 5 simple “yes/no” questions. The first 4 incorporate the prerequisites for a diagnosis of generalized acquired

DECREASED SEXUAL DESIRE SCREENER BRIEF DIAGNOSTIC ASSESSMENT FOR GENERALIZED, ACQUIRED HSDD		
THE DECREASED SEXUAL DESIRE SCREENER (DSDS) IS INTENDED TO ASSIST YOUR CLINICIAN IN THE ASSESSMENT OF YOUR DECREASED SEXUAL DESIRE. PLEASE ANSWER EACH OF THE FOLLOWING QUESTIONS BY CIRCLING EITHER YES OR NO.		
1	In the past, was your level of sexual desire or interest good & satisfying to you?	Yes / No
2	Has there been a decrease in your level of sexual desire or interest?	Yes / No
3	Are you bothered by your decreased level of sexual desire or interest?	Yes / No
4	Would you like your level of sexual desire or interest to increase?	Yes / No
5	Please circle all of the factors that you feel may be contributing to your current decrease in sexual desire or interest:	
	a. An operation, depression, injuries, or other medical condition	Yes / No
	b. Medications, drugs, or alcohol you are currently taking	Yes / No
	c. Pregnancy, recent childbirth, menopausal symptoms	Yes / No
	d. Other sexual issues you may be having (pain, decreased arousal or orgasm)	Yes / No
	e. Your partner's sexual problems	Yes / No
	f. Dissatisfaction with your relationship or partner	Yes / No
	g. Stress or fatigue	Yes / No

FIGURE 2. Decreased Sexual Desire Screener. From *J Sex Med*,³² with permission from Elsevier.

HSDD: (1) previous satisfaction with her desire/interest in sex, (2) a decrease from prior satisfaction, (3) bother by the decline in sexual desire, and (4) wish for improvement in her sexual desire.^{26,32} Responses of no previous satisfaction with her desire/interest in sex, and therefore no decrease from prior satisfaction, would be consistent with lifelong low sexual desire/interest. In the fifth query, the patient is asked to identify with “yes/no” responses which, if any, of the 7 listed groups of factors might apply to her situation, potentially having an adverse effect on her sexual desire/interest (Figure 2).³² Low sexual desire and the associated distress and behavioral adaptations may impact the partner relationship, or problems in the partner relationship may contribute to low desire.

If a woman responds “no” to at least 1 of the first 4 questions, she does not meet criteria for generalized acquired HSDD but could meet criteria for either situational or lifelong low

sexual desire/interest. If the patient answers “yes” to questions 1 through 4 and “no” to all the factors in question 5, she has generalized acquired HSDD. If any of the factors in question 5 are present, the HCP must evaluate and consider differential diagnoses including biological etiologies of low desire, as well as decide whether the responses to question 5 indicate generalized acquired HSDD or situational low sexual desire/interest. Situational loss of desire may occur in response to a temporary stressful life situation. Individuals with no/low sexual interest over their lifetime and who are not distressed may be asexual and as such do not meet criteria for HSDD, and no intervention is indicated.³⁶ Comorbid conditions such as arousal and orgasmic disorder do not rule out a concurrent diagnosis of HSDD.

If the DSDS suggests the diagnosis of low sexual interest without distress, distressing lifelong sexual desire, or situational low sexual desire, the HCP should consider strategies that

TABLE 1. Physical Examination to Evaluate Other Factors Contributing to Decreased Desire

Condition	Assessment
Clitoral adhesions/phimosis or clitoral atrophy	Visual examination under magnification
Urethral meatal prolapse, telescoping of urethral meatus	Visual examination under magnification
Vulvodynia	Assess sensitivity to pressure with cotton swab around vestibule from 11-o'clock to 1-o'clock positions
High-tone pelvic floor dysfunction	Manual examination
Labial resorption; vulvar, vestibular, or vaginal atrophy	Visual examination under magnification, vaginal smear (wet mount)
Vulvar dystrophies and dermatoses	Visual examination under magnification, biopsy if needed
Pudendal nerve disorder	Assess tenderness at ischial spine, assess tenderness of pelvic floor muscles
Lumbar-sacral spinal pathology	Quantitative sensory testing, bulbocavernosus reflex latency testing, magnetic resonance imaging of lumbar and sacral spine

engage education and/or counseling or referral to a specialist. In those with generalized acquired HSDD, the HCP may elicit a sexual history or proceed with the POC. In summary, the DSDS offers the HCP a quick, nonthreatening way to screen for and diagnose HSDD in the clinical setting and begin to identify modifiable factors/etiologies.³²

Sexual History

In addition to the DSDS, the HCP may also conduct a sexual history. This may include past and present characteristics of the patient's sexual desire/interest and other aspects of sexual function such as arousal, orgasmic function, and/or any pain/discomfort during sexual activity. Sexual function may be assessed with regard to either partnered or unpartnered sexual activity and may include a history of her past and present partner relationships and sexual experiences. If a sexual desire discrepancy exists between the patient and her partner, it may only be considered HSDD if the desire discrepancy causes her distress.⁹ The evaluation may also include a brief psychosocial assessment because sexual dysfunction may affect the patient's self-esteem and coping ability, as well as her social and occupational role performance.

When a woman endorses distressing low sexual desire, the interview should proceed with questions related to the diagnosis of HSDD including: low motivation for participation in sexual activity, loss of spontaneous sexual desire (including sexual thoughts and

fantasies), lack of desire in response to erotic cues and stimulation, low initiation and avoidance of situations that could lead to sexual activity, and participation in sexual activity due to obligation or fear of losing her partner.²⁶

BIOPSYCHOSOCIAL ASSESSMENT OF POTENTIAL MODIFIABLE FACTORS

For women with a diagnosis of generalized acquired HSDD, HCPs should next obtain a history, perform a physical examination as considered appropriate, and order blood testing when indicated to clarify any modifiable factors.

Physical Examination

A general physical examination of patients who experience HSDD has a low diagnostic yield and does not identify the specific cause of the HSDD in most cases. However, a focused examination, including a pelvic examination with assessment of the vulvar and vaginal tissue, may be appropriate if indicated (Table 1). A physical examination may also reveal signs of hormone insufficiency states.²⁶ The physical examination also provides an excellent opportunity for patient education and reassurance regarding normal genital anatomy. The findings on this examination may be used to identify referral needs.

Laboratory Testing

Laboratory and imaging investigations are dictated by the woman's medical history and physical examination findings. Because there

TABLE 2. Recommended Blood Tests for Further Investigation if HSDD Is Concurrent With Oligomenorrhea or Amenorrhea and/or Galactorrhea

Hormone	Possible conditions	Level of evidence
Prolactin	Hyperprolactinemia causing ovarian suppression and low sex steroid production ^{37,38}	3
Thyroid function panel	Hypothyroidism ³⁹ or hyperthyroidism ⁴⁰	2-3
Estradiol, progesterone, luteinizing hormone, testosterone, sex hormone-binding globulin	Oligomenorrhea or amenorrhea ^{5,37,41}	2-3

are no biomarkers that confirm or exclude HSDD, laboratory testing—specifically, measurement of testosterone—should not be used to make the diagnosis. Other hormone assays may be considered if there is concern about comorbid conditions contributing to low desire, although this testing is not clinically indicated on a routine basis (Table 2).^{5,37-41} These tests are primarily performed to identify specific etiologies or to assess the role of concomitant medical conditions. Referral to a specialist in sexual medicine may be considered if a more specialized physical examination, testing, or treatment is needed. Reasons for referral may include primary/lifelong and/or situational low desire, relationship problems, physical or psychological trauma, endocrinopathy, complex medical problems, or treatment failures.⁴²

When a woman presents with HSDD without any potentially causative comorbidity or relationship conflict, the diagnosis of HSDD without a modifiable cause can be established. In this case, menopausal status should be assessed according to the STRAW + 10 (Stages of Reproductive Aging Workshop) classification system in order to guide therapeutic decision making.⁴³

MODIFIABLE FACTORS

The evaluation for HSDD should include screening for other sexual problems related to arousal, orgasm, and pain⁹ in order to determine the primary vs secondary problem(s) by assessing the temporal relationship of the onset of these complaints relative to the onset of low desire. It is also necessary to determine if HSDD is lifelong or acquired and generalized (occurs in all settings with all partners) or situational. Other key areas of inquiry should include prior sexual functioning and relationship/interpersonal

issues.⁴⁴⁻⁴⁷ It is important to note that a woman can experience HSDD and not be in a stable relationship (ie, has no partner or multiple serial partners).¹⁹

The HCP should ask specifically about other sexual problems that might exacerbate low desire and influence the management and eventual success of treatment. In the Hypoactive Sexual Desire Disorder Registry for Women study, a large observational study of US women with clinically diagnosed generalized acquired HSDD, arousal disorders, lubrication problems, or both were reported by 50.2%, 42.5%, and 39% of women with HSDD, respectively.^{48,49} A list of some potentially useful screeners and questionnaires is provided in the Supplemental Table (available online at <http://www.mayoclinicproceedings.org>).

In patients with generalized acquired HSDD, elicitation of the medical history should include questions about psychiatric conditions, medical problems, and menopausal status (Table 3)⁵⁰⁻⁵³ and relevant medications and misuse/abuse of substances (Table 4).⁵⁴

The assessment should include a medical, psychological, and social history to identify any factors that may be potentially reversible. Obtaining a detailed gynecologic history is important with particular attention to menstrual cycles in premenopausal women; symptoms of the genitourinary syndrome of menopause;⁵⁵ pelvic floor disorders such as urinary incontinence, fecal incontinence, prolapse, and high-tone pelvic floor dysfunction; and menopausal vasomotor symptoms, because each of these factors has been associated with lowered sexual desire.^{15,19,56,57}

Bilateral salpingo-oophorectomy before natural menopause is associated with an increased likelihood of HSDD.¹² Bilateral salpingo-oophorectomy at any age is associated

TABLE 3. Medical Conditions Potentially Impacting Sexual Function^{a,b}

Medical Condition	Desire	Arousal	Orgasm	Pain	Comments
Coronary artery disease	–	+	–	–	None
Hypertension	+	–	–	–	Impact of hypertension or treatment is unclear; one study found an association with low desire
Diabetes	+	–	–	–	Low desire may relate to depression and relationship status
Metabolic syndrome	+	+	+	–	None
Hypothyroidism	–	+	+	–	Increased problems with lubrication and orgasm
Pituitary tumor/hyperprolactinemia	+	–	–	–	None
Urinary incontinence	+	+	–	+	None
Renal failure	–	–	–	–	Dialysis associated with sexual dysfunction
Spinal cord injury/multiple sclerosis/neuromuscular disorders	+	+	+	+	Direct impact on sexual response; indirect effect on desire may be mediated by arousal disorders/pain
Parkinson disease/dementia/head injury	+	–	–	–	Desire may be increased or decreased
Arthritis	–	–	–	+	Decreased mobility and chronic pain may impair sexual function
Dermatological conditions (vulvar lichen sclerosus, vulvar eczema, psoriasis, Paget disease)	–	–	–	+	None
Gynecologic conditions (genitourinary syndrome of menopause, sexually transmitted infections, endometriosis, chronic pelvic pain, childbirth, pelvic organ prolapse)	–	–	–	+	None
Malignancy and treatment (breast, anal, bladder, colorectal, and gynecologic cancers)	+	+	+	+	Sexual function may be directly or indirectly impacted by cancer diagnosis and treatment. Factors include cancer diagnosis, disease itself, treatment (surgery, radiation, chemotherapy), and body image
Major depression	+	+	+	–	None

^a+ = affected; – = not affected.
^bData from references 50-52.
Adapted from *Am Fam Physician*,⁵³ with permission.

with lower total and free testosterone levels.⁵⁸⁻⁶² Women should be asked about other pelvic operations, trauma, or radiotherapy because these factors may be associated with pelvic pain and altered ovarian function. Other conditions associated with lower androgen levels, and potentially diminished desire, include hyperprolactinemia,^{63,64} hypopituitarism, hypothalamic amenorrhea, adrenal insufficiency, primary ovarian insufficiency, and chemical ovarian suppression. Conditions that may increase sex hormone–binding globulin (SHBG) levels, and hence lower free testosterone levels, include hyperthyroidism and human immunodeficiency virus infection.⁶⁵ Overt^{66,68} or subclinical^{66,69} hypothyroidism

and hyperthyroidism have been associated with reduced sexual desire.^{68,70} Conversely, polycystic ovary syndrome is often characterized by clinical and/or biochemical signs of hyperandrogenism, with or without oligoovulation or anovulation, or polycystic ovaries. Women with polycystic ovary syndrome have psychological (feeling less attractive, less feminine, more depressed) and biological (obesity and infertility) factors that may negatively influence their sexual desire.⁷¹

Depressive symptoms are independently and bidirectionally associated with HSDD, with the presence of depression conferring a 50% to 70% increased risk of sexual dysfunction, and the occurrence of sexual dysfunction

is associated with a 130% to 210% increased risk of depression.^{19,72} Adding a layer of complexity, most antidepressants are associated with decreased sexual desire⁷³⁻⁷⁶; therefore, use of antidepressant medication may actually substitute one causative factor of HSDD for another. The Patient Health Questionnaire (PHQ)⁷⁷ is a validated instrument to screen for and monitor severity of depressive symptoms. In the Hypoactive Sexual Desire Disorder Registry for Women study, 34% of a clinical sample of women with acquired, generalized HSDD were found to have concurrent symptoms of depression as measured by the PHQ-9 or were being treated with antidepressant medications; however, 58% had not been diagnosed or treated for depression before entering the study.⁷⁸ In the general population PRESIDE study, 37% of women had concurrent depression as identified either by the PHQ-9, prior diagnosis of depression, or treatment with antidepressant medications.⁷⁹ Given this significant comorbidity, every patient with HSDD should be screened for depressive symptoms because major depressive disorder or treatment with an antidepressant medication may be a modifiable etiologic factor [LoE 2]. It is important to note that depression is also associated with significant chronic medical conditions such as diabetes.⁸⁰

Both type 1 and type 2 diabetes mellitus almost double the risk of sexual dysfunction.⁸¹ In the Epidemiology of Diabetes Interventions and Complications study, 57% of women with type 1 diabetes reported low sexual desire.⁸² Interestingly, the prediabetic state (slightly elevated blood glucose levels) was also characterized by impairment of sexual desire and sexual satisfaction.⁸³ Reduced sexual desire and sexual satisfaction were strongly associated with insulin resistance (Homeostatic Model Assessment Index 1—Insulin Resistance) and therefore susceptible to changes in insulin sensitivity.⁸³

Metabolic syndrome (MetS) is a group of cardiovascular risk factors: high blood pressure, elevated blood glucose level, abnormal cholesterol levels, and abdominal obesity. Data for a relationship between MetS and HSDD are conflicting. In a study of 376 postmenopausal community-dwelling women, those with MetS had significantly lower sexual

TABLE 4. Medications Associated With Female Sexual Dysfunction

Medication	Desire disorder	Arousal disorders	Orgasm disorders
Anticholinergics	–	+	–
Antihistamines	–	+	–
Amphetamines and related anorexic drugs	–	–	+
Cardiovascular and antihypertensive medications			
Antilipid medications	+	–	–
β-Blockers	+	–	–
Clonidine	+	+	–
Digoxin	+	–	+
Spironolactone	+	–	–
Methyldopa	+	–	–
Hormonal preparations			
Danazol	+	–	–
GnRH agonists	+	–	–
Hormonal contraceptives	+	+	–
Antiandrogens	+	+	+
Tamoxifen	+	+	–
GnRH analogues	+	+	–
Ultralight contraceptive pills	+	+	–
Narcotics	+	–	+
Psychotropics			
Antipsychotics	+	+	+
Barbiturates	+	+	+
Benzodiazepines	+	+	–
Lithium	+	+	+
SSRIs	+	+	+
TCA	+	+	+
MAO inhibitors	–	–	+
Venlafaxine	+	+	+
Other			
Histamine 2 receptor blockers and promotility agents	+	–	–
Indomethacin	+	–	–
Ketoconazole	+	–	–
Phenytoin sodium	+	–	–
Aromatase inhibitors	+	+	–
Chemotherapeutic agents	+	+	–

GnRH = gonadotropin-releasing hormone; MAO = monoamine oxidase; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; + = yes; – = no. Adapted from *Fertil Steril*,⁵⁴ with permission from Elsevier.

desire compared with other women.⁸⁴ Three smaller case-control studies did not find any significant association between MetS and sexual desire.⁸⁵⁻⁸⁷ Whereas in population-based studies sexual desire is inversely associated with body mass index,⁸⁸⁻⁹⁰ 3 clinical studies of women seeking or undergoing weight loss treatment did not find an increase in sexual desire.⁹¹⁻⁹³ However, observational studies have consistently indicated a trend toward improvement in sexual desire after weight loss,^{94,95} potentially due to improved body image. Both obesity and MetS have been

associated with increased baseline clitoral vascular resistance and impaired sexual arousal, suggesting that the negative impact of these metabolic phenotypes on sexual function is primarily at the genital level rather than a central effect.⁹⁶

Various neurologic diseases have been associated with decreased sexual desire, notably multiple sclerosis^{97,98} and spinal cord injury,⁹⁹ but data are limited.

Decreased sexual desire is a common issue for women after a diagnosis of breast cancer, ranging from 23% to 80% of women.^{100,101} Sexual problems are independently associated with being postmenopausal (potentially provoked by chemotherapy), having vasomotor symptoms, and taking an aromatase inhibitor (AI).^{101,102} Chemotherapy increases the likelihood of sexual complaints compared with surgery and/or radiation.¹⁰³ In addition, AI therapy is associated with vaginal dryness, dyspareunia, and decreased sexual desire.^{102,104}

Medications that lower testosterone production include combined hormonal contraceptives (CHCs; oral, transvaginal, and transdermal),¹⁰⁵ chemical ovarian suppression by gonadotropin-releasing hormone analogues, and pharmacological glucocorticoid administration. Some other compounds exhibit antiandrogen activity (spironolactone, cyproterone acetate, flutamide, and finasteride). Drugs increasing SHBG levels, and hence lowering free testosterone levels, also include oral estrogens, CHCs, tamoxifen, and thyroxine.⁶⁵ A double-blind, placebo-controlled, randomized trial determined that a levonorgestrel-containing oral contraceptive lowers sexual desire in comparison with placebo.¹⁰⁶ Even though all CHCs suppress ovarian testosterone production, the greatest increase in SHBG level is seen with the higher ethinyl estradiol doses (30-35 µg) and with third- or fourth-generation progestins.¹⁰⁵ A recent study found evidence for a role of the CAG repeat length of the androgen receptor on the sexual desire of contraceptive users.¹⁰⁷ In addition, drugs that may elevate prolactin levels and, in part, decrease sexual desire include antipsychotics and others.^{38,108} We conclude that CHCs may be associated with HSDD in some women, and thus, change of medication may improve desire [LoE 2].

TREATMENT

Therapeutic strategies for this POC include education and, if needed, addressing modifiable factors. Should generalized acquired HSDD persist, treatment may include sex therapy, central nervous system (CNS) agents, and hormonal agents, taking into account menopausal status.

First- and Second-Line Therapies

Education. Effective patient education requires knowledge, time, communication skills, and bibliographic resources that facilitate positive sexual behavioral changes.⁴³ Education may be structured in 3 parts. First, provide information on normal sexual functioning. This information may include a description of spontaneous and responsive sexual desire, the role of motivation in sexual desire, the importance of adequate sexual stimulation, the impact of pleasurable sexual experiences on desire, and the influence of age and relationship duration.¹⁰⁹⁻¹¹¹ Second, educate the patient about factors that are derived from the sexual and medical history that may disrupt sexual desire (eg, mood disorders, relationship satisfaction, body image).⁵ Third, HCPs may assess motivation for treatment and discuss treatment options.^{5,112} If the patient has a partner, involving the partner in treatment may sometimes be helpful. Education should continue throughout the process, including patient follow-up.

Modification of Potentially Contributing Factors.

The next intervention level includes modification of factors thought to be playing a role in HSDD. The following paragraphs summarize strategies for intervention for some of the more common modifiable factors associated with HSDD and are based on consensus expert opinion.

Treatment of genital arousal symptoms and pain with vaginal lubricants, vaginal moisturizers, low-dose vaginal estrogen or intravaginal dehydroepiandrosterone (DHEA),¹¹³ or physical therapy (for hypertonic, tender pelvic floor muscles)^{114,115} and menopausal vasomotor symptoms with systemic hormone therapy¹¹⁶ may relieve symptoms and therefore improve desire. In particular, pain with sexual activity should be addressed before treatment of HSDD.

In women with type 2 diabetes, limited evidence suggests that lifestyle modifications that include substantial weight loss may

TABLE 5. Psychological Factors and Treatment Strategies

Psychological factor	Recommended approach
Depression/anxiety	Pharmacotherapy/cognitive behavioral therapy
Poor self-esteem/body image	Psychotherapy
Stress/distraction	Cognitive behavioral therapy
History of abuse (physical, sexual, emotional)	Psychotherapy
Substance abuse	Psychotherapy
Self-imposed pressure for sex	Office-based counseling or refer for cognitive behavioral therapy
Religious, personal, cultural or family values, beliefs, and taboos	Office-based counseling or refer for cognitive behavioral therapy
Relationship factors	Office-based counseling or refer for individual/couples therapy
Lifestyle factors (eg, fatigue, sleep deprivation)	Office-based counseling
Sexual factors (eg, inadequate stimulation)	Office-based counseling

alleviate sexual dysfunction.³⁷ Treatment of gynecologic disorders and urinary or fecal incontinence may positively impact sexual desire.^{50,51} Malignant disorders may adversely affect sexual function either directly, as the result of the disorder itself, or indirectly, related to the cancer diagnosis or treatment, and addressing sexual changes resulting from cancer or treatment may lead to improved sexual function.¹¹⁷

Sleep problems and insomnia in particular are common concerns among women. In the Women's Health Initiative Observational Study, higher insomnia scores and shorter durations of sleep (<7-8 hours) were associated with decreased sexual function.¹¹⁸ Improving duration and quality of sleep may positively affect sexual function.

As noted previously, depression has a bidirectional association with sexual dysfunction, and adequate treatment of depression may positively impact sexual function.^{5,72} Additionally, antidepressant medications are commonly associated with treatment-emergent sexual dysfunction, a potential adverse effect that may result in discontinuation of treatment and impaired quality of life.^{75,119,120} Management strategies for antidepressant-related sexual dysfunction include behavioral (eg, exercise, scheduling sexual activity, vibratory stimulation),^{121,122} complementary (eg, acupuncture),¹²³ and pharmacological (eg, dose reduction or discontinuation, switching to a drug with fewer sexual adverse effects, and adding antidotes/adjunctive treatment) therapies.¹²⁴⁻¹²⁷ Other commonly used medications potentially impacting sexual function include CHCs, AIs, and spironolactone.⁵⁴ Reviewing a patient's medication list

and modifying medication regimens potentially impacting sexual function (Table 4) may improve sexual desire. Alcohol, smoking and illicit substance use may also contribute to sexual dysfunction.

Several psychological factors that may contribute to loss of sexual desire may be modifiable. Table 5 lists the most common psychological factors contributing to HSDD. Relationship factors frequently adversely impact sexual desire. Health care professionals may use office-based counseling or may consider referring the patient to an individual or couples therapist to modify negative communication patterns, to address partner sexual dysfunction, to modify the partner's pressure or demanding behavior for sex, and to help problem solve when lack of time and/or privacy are contributing factors.⁵¹ Office-based counseling may also be useful to reevaluate and alter interfering beliefs and values¹²⁸ and should be continued in follow-up.

Third-Line Treatment Options

Sex Therapy. A range of psychological interventions has been developed to treat sexual dysfunctions in women, independent of menopausal status. Focused sex therapy for HSDD is unlikely to be effective if relationship problems contributing to low desire or as a result of HSDD (ie, power, control, trust) for women with a partner, sexual dysfunction in the partner, or a history of sexual, physical, or emotional abuse are not addressed.

Three frequently used psychological interventions are behavior therapy, cognitive behavior therapy (CBT), and mindfulness therapy. Behavior therapy attempts to alleviate

sexual difficulties through a combination of techniques including education, communication skills training, and sensate focus exercises.^{129,130} On their own, sensate focus exercises are unlikely to be effective for HSDD in women [LoE 5].

Cognitive behavior therapy is designed to challenge unrealistic beliefs that may be contributing to sexual problems and to alter behaviors that maintain HSDD. For example, individuals may be making cognitive errors, personalizing, or catastrophizing.¹³¹ With the help of the therapist, the patient learns to identify and challenge the unrealistic beliefs that trigger negative behaviors and emotions regarding sexual activity. A meta-analysis of 20 small studies using psychological interventions vs a wait-list control in multiple settings in the treatment of various types of sexual dysfunctions in men and women (4 of the 20 studies were of HSDD in women)¹³² found that psychological interventions were effective in reducing symptom severity and, to a lesser degree, improving sexual satisfaction among women with low sexual desire [LoE 1]. A more recent, more specific review¹³³ found 3 studies in which CBT in women with HSDD was effective vs wait-list controls.

Mindfulness-based CBT includes exercises that aim to cultivate present-moment awareness and nonjudgmental observation of experiences.¹³⁴⁻¹³⁶ When applied to HSDD, mindfulness exercises may help decrease cognitive distraction during sexual activity and increase awareness of pleasurable sensations.¹³⁶⁻¹³⁹ Two wait-list controlled studies support mindfulness meditation training in women with HSDD.¹³³ To date, 5 studies have evaluated the incorporation of mindfulness training into a CBT intervention for women with non-HSDD female sexual problems¹⁴⁰⁻¹⁴⁴ and found improvements in sexual desire and related distress. Mindfulness therapy has demonstrated preliminary levels of effectiveness in the treatment of this disorder among women.¹⁴⁴⁻¹⁴⁶

CNS Agents. Flibanserin is currently the only US Food and Drug Administration–approved medication for generalized acquired HSDD in premenopausal women. Flibanserin (100 mg dosed at bedtime) is a nonhormonal, centrally acting, daily, oral, multifunctional serotonin

agonist and antagonist.¹⁴⁷ Efficacy was established in 3 pivotal trials in more than 3500 women, demonstrating a statistically significant and clinically meaningful improvement in the level of sexual desire and the number of sexually satisfying events and a decrease in distress compared with placebo [LoE 1].¹⁴⁸⁻¹⁵⁰

Clinical trials of flibanserin in postmenopausal women have found similar efficacy, but it is not currently Food and Drug Administration–approved in this population.¹⁵¹ Approximately 50% of women with HSDD respond to flibanserin, and it may take up to 8 weeks for efficacy to emerge. The most common adverse events (AEs) in premenopausal women are dizziness (9.2%), somnolence (8.3%), nausea (6.5%), and fatigue (3.7%)¹⁴⁷; placebo-corrected rates are similar to other CNS-active agents. Most AEs are mild, transient, and mitigated with bedtime dosing. In the trials, discontinuation due to AEs was 13% in premenopausal women treated with flibanserin compared with 6% with placebo.

Flibanserin labeling has a boxed warning that concomitant alcohol use is contraindicated on the basis of the results of an alcohol challenge study that found an increase in sedation, syncope, and hypotension in the treatment group (23 men and 2 women).¹⁵² However, alcohol use was not restricted and did not increase such AEs over placebo in the 3 major pivotal trials that were limited to premenopausal women.¹⁵³ A postapproval alcohol interaction study performed in 96 women (≤ 45 years old) revealed no effect of concomitant ethanol ingestion for somnolence, drowsiness, orthostatic blood pressure, vertigo, or hypotension with no reports of syncope, although a small increase in dizziness was reported at the highest dose of ethanol (0.6 g/kg) when taken with flibanserin (39.8%) compared with flibanserin alone (31.3%).¹⁵² A risk evaluation and mitigation program requires certification of prescribers and pharmacies in consenting patients to avoid alcohol.

Other CNS-active agents approved for other indications have been used off-label for the treatment of HSDD despite limited efficacy and safety data. Bupropion, which acts to enhance dopamine and norepinephrine, was found in a randomized, double-blind, placebo-controlled trial (at 300-400 mg/d) to improve sexual desire vs placebo in women

with HSDD, but enrollment was insufficient to reach statistical significance, as prespecified in the study protocol [LoE 2].¹⁵⁴ Adverse effects of bupropion used for treatment of major depression or smoking cessation include tremor (13.5%), agitation (9.7%), dry mouth (9.2%), constipation (8.2%), dizziness (6.1%), and nausea/vomiting (4%).¹⁵⁵ In women with antidepressant-induced sexual dysfunction, the addition of sustained-release bupropion (300 mg/day) improved sexual desire vs placebo.¹²⁵

Bupirone, which reduces serotonin inhibition, is another off-label treatment that has been used for antidepressant-associated sexual dysfunction. One trial found improvement in sexual function (including “low libido”) in depressed women with selective serotonin reuptake inhibitor–induced sexual dysfunction with bupirone (30-60 mg/d) compared with placebo (58% vs 30%) [LoE 2].^{6,156} The most common adverse effects of bupirone in studies of generalized anxiety disorder (approved indication) are dizziness (9%), nervousness (4%), nausea (3%), and headache (3%).

Drug development research for HSDD has been directed toward finding CNS agents that specifically activate stimulatory pathways or reduce inhibitory pathways regulating sexual desire.¹⁵⁷ Therapies in clinical trial development include bremelanotide¹⁵⁸⁻¹⁶⁴ and combination therapies: testosterone with sildenafil and testosterone with bupirone¹⁶⁵⁻¹⁶⁷ and bupropion with trazodone.¹⁶⁸

Hormonal Therapy. Testosterone therapy was initially approved in Europe for the treatment of HSDD in surgically menopausal women and is currently approved in Australia for women with testosterone deficiency and associated symptoms such as low sexual desire. However, testosterone therapy in women remains an off-label treatment in other countries. Oral testosterone therapy is not recommended because there are substantial intraindividual and interindividual variations in absorption such that levels achieved are often supraphysiologic and may result in lipid/cardiac effects and hepatotoxicity.¹⁶⁹ Studies using transdermal testosterone have consistently revealed efficacy for the treatment of HSDD in both naturally and surgically

postmenopausal women, either alone or in combination with menopausal estrogen therapy [LoE 1].^{26,65,170} Four published 24-week phase 3 clinical trials in naturally and surgically postmenopausal women with HSDD found that a 300- μ g/d testosterone patch significantly improved the primary efficacy measures of sexual desire and frequency of satisfying sexual events (measured by proprietary instruments) vs placebo.¹⁷¹⁻¹⁷⁴ Levels of sexually related distress also decreased significantly compared with placebo in 3 of the 4 studies.

The most common AEs in descending order were application site reactions, acne, breast pain, headache, and hirsutism. Laboratory findings (liver function and hematologic tests, lipid profiles, clotting measures, and carbohydrate metabolism) remained essentially unchanged from baseline and did not differ among treatment groups.¹⁷¹⁻¹⁷⁶ In postmenopausal women, when serum free testosterone is maintained within the normal range for premenopausal women, short-term safety data are reassuring [LoE 1].^{170,177,178} However, the long-term safety of testosterone use in postmenopausal women is limited to observational studies.¹⁷⁹ Likewise, long-term (beyond 2 years) safety data with regard to breast cancer and cardiovascular events are limited to observational trials and are inconclusive.^{171,176,179,180} Studies involving reproductive-aged women are lacking.

If testosterone therapy is being considered (at the discretion of the patient and the HCP), baseline and follow-up testosterone values may be assessed [LoE 2-3].²⁶ Normal testosterone ranges have been reported for women of different age groups, but there is no minimal value for any androgen that can be used to identify women with HSDD.^{65,181} Most circulating testosterone is bound to proteins (ie, SHBG, albumin), and only 1% to 2% of the total testosterone is unbound or free and biologically active.⁶⁵ Sex hormone–binding globulin levels vary considerably among individuals⁵⁸ and may be increased by oral estrogens, hormonal contraception, and thyroid hormone replacement and lowered by central adiposity and oral androgen therapy.^{181,182} Most radioimmunoassays lack the precision to accurately measure total testosterone levels in women¹⁸³ such that, when possible, testosterone should be measured by liquid

HYPOTHESIS: IN WOMEN WITH HSDD - THE EFFECT OF TREATMENTS ON SEXUAL DESIRE

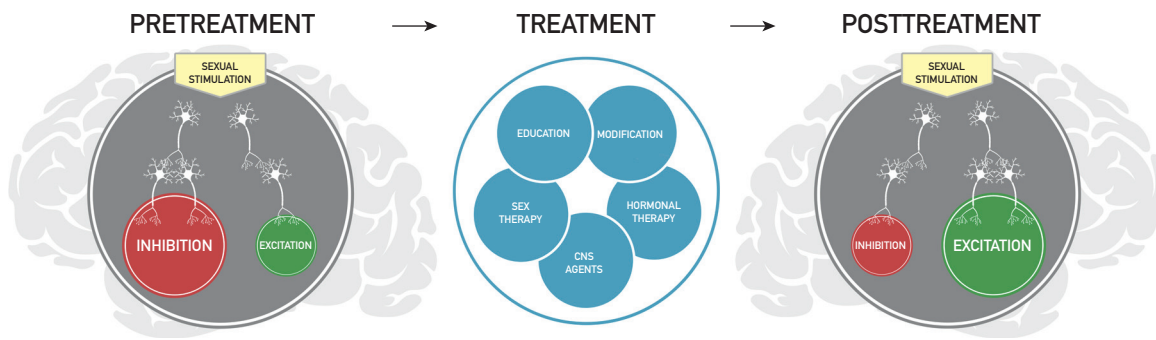


FIGURE 3. Hypothetical impact of treatments for hypoactive sexual desire disorder (HSDD). Although the precise etiology of HSDD remains unknown, the activities of inhibitory brain neurotransmitters (opioids, serotonin, and endocannabinoids) are thought to be greater than the activities of excitatory brain neurotransmitters (dopamine, melanocortin, oxytocin, vasopressin, and norepinephrine) in the presence of sexual cues and stimuli. Although the initial molecular mechanisms may vary, sex therapy, central nervous system agents, or hormonal agents used in treating HSDD may ultimately cause similar underlying changes in brain function and structure within neural circuits that regulate sexual desire such that excitation systems can be activated to a greater extent than inhibitory systems in the presence of cues and stimuli.

chromatography—mass spectrometry, which is increasingly becoming available to clinicians.¹⁸⁴ Free testosterone levels can be calculated from measured total testosterone and SHBG levels using an online calculator.¹⁸⁵ Women using testosterone should have regular follow-up blood testosterone measurements to ensure that supraphysiologic therapy is avoided.¹⁷⁰

Testosterone formulations for women are not globally available, so clinicians are commonly limited to prescribing compounded formulations or testosterone formulations for men modified to much lower administered doses (usually one-tenth of the male dose) because supraphysiologic concentrations can cause virilization [LoE *Expert opinion/clinical principle*].^{65,170} When a trial of testosterone therapy is initiated, treatment should be discontinued if the patient experiences no improvement in symptoms after 6 months.¹⁷⁰

The synthetic orally active steroid tibolone is weakly androgenic and lowers SHBG, resulting in an increase in endogenous free testosterone.¹⁸⁶ Although a small randomized clinical trial of women with sexual dysfunction found tibolone to be marginally more effective for low desire than transdermal hormone

therapy,¹⁸⁷ a recent meta-analysis failed to confirm tibolone's benefit on sexual desire in postmenopausal women [LoE 2-3].¹¹⁶

Concerning oral DHEA, systematic reviews and meta-analyses have found no statistically significant benefit of systemic DHEA on female sexual dysfunction [LoE 1].¹⁸⁸

Follow-up and Reassessment

Reassessment and follow-up should be conducted at regular intervals at the discretion of the HCP. This step facilitates patient communication including discussion regarding other problems, patient concerns regarding treatment (eg, adverse drug reactions), and other sexual dysfunctions such as pain, partner issues, or lifestyle factors such as emotional distress. Patients may change medication regimens for other conditions that may impact treatment of HSDD. The need for dosage titration or substitution of one therapy for another may be considered at each follow-up visit. Patients may change treatment preferences, seek new information, or wish to reevaluate their current treatment regimen. Lastly, general medical and psychosocial reassessment should occur at regular intervals, depending on the health and

psychosocial needs of the patient. Follow-up is intended to monitor the progress of therapy and the medical status of the patient (and partner) and provides an opportunity for further patient education.

DISCUSSION

The management steps within this POC are dependent on first asking about sexual health concerns, then distinguishing among the sexual dysfunctions to identify women with HSDD, and finally making the appropriate selection of treatment options. Treatments may include education, addressing potentially modifiable factors, psychological therapy, CNS agents, or hormone therapy. Management principles include taking into account risk to benefit ratio, degree of invasiveness, and cost in order to provide individualized care. The final decision with regard to treatment is most often dependent on patient (and partner) preferences and goals. This factor is clinically relevant considering the lack of comparison data to prioritize these therapies for HSDD.

Although the precise mechanisms for any given treatment may vary, we hypothesize that all effective treatments for HSDD result in functional changes in the neural pathways regulating sexual desire in order to enable excitation to overcome inhibition in the appropriate context of spontaneous sexual thoughts and/or visual/aural/physical stimulation (Figure 3). This hypothesis is consistent with studies demonstrating neuroplastic alterations regulating neurogenesis, synaptic plasticity, and synaptic activity associated with all of the recommended interventions: mindfulness and cognitive behavioral therapy,¹⁸⁹⁻¹⁹² steroid hormones,^{193,194} and CNS-active drugs that modulate the neurotransmitter systems mediating HSDD.¹⁹⁵⁻¹⁹⁷

Given the unmet need of women with HSDD, developmental efforts are continuing for new safe and effective treatments. However, cost of development and regulatory requirements remain substantial obstacles. It should be emphasized that the impact of any drug therapy is not to circumvent the inhibitory influence on sexual desire that normally predominates. Rather, modulation of neuroendocrine systems may facilitate the activation of

sexual desire pathways when both physiologic stimulation and social context are sufficient and appropriate.

This ISSWSH POC is an international consensus guideline to help HCPs in the management of women with HSDD. Health care professionals are encouraged to initiate a conversation with their patients about sexual activity and sexual satisfaction. Asking about these issues using the techniques noted in this POC can demonstrate a deeper interest on the part of the HCP in aspects of life that may be extremely important to patients. The depth of the inquiry can depend on the interests and depth of experience of the HCP. Self-recognition of an HCP's clinical and practice limitations can result in appropriate referral of a woman for a distressing problem, both empowering the patient and leading to successful outcome.

CONCLUSION

The ISSWSH POC provides guidelines for clinicians caring for women to diagnose HSDD and provide management, taking into account all the contributing biopsychosocial aspects: physical, medical, and medication factors; relationship and life situations; and personal sexual behaviors and history in order to provide education, modification of existing factors, and treatment based on shared decision making between the patient and her HCP. The ultimate goal of all treatment programs is improved function via a working partnership between the patient and her HCP.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AE** = adverse event; **AI** = aromatase inhibitor; **CBT** = cognitive behavior therapy; **CHC** = combined hormonal contraceptive; **CNS** = central nervous system; **DHEA** = dehydroepiandrosterone; **DSDS** = Decreased Sexual Desire Screener; **HCP** = health care professional; **HSDD** = hypoactive sexual desire disorder; **ISSWSH** = International Society for the Study of Women's Sexual Health; **LoE** = level of evidence; **MetS** = metabolic syndrome; **PHQ** = Patient Health Questionnaire; **POC** = process of care; **SHBG** = sex hormone-binding globulin

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The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women

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Abstract

The International Society for the Study of Women's Sexual Health process of care (POC) for management of hypoactive sexual desire disorder (HSDD) algorithm was developed to provide evidence-based guidelines for diagnosis and treatment of HSDD in women by health care professionals. Affecting 10% of adult females, HSDD is associated with negative emotional and psychological states and medical conditions including depression. The algorithm was developed using a modified Delphi method to reach consensus among the 17 international panelists representing multiple disciplines. The POC starts with the health care professional asking about sexual concerns, focusing on issues related to low sexual desire/interest. Diagnosis includes distinguishing between generalized acquired HSDD and other forms of low sexual interest. Biopsychosocial assessment of potentially modifiable factors facilitates initiation of treatment with education, modification of potentially modifiable factors, and, if needed, additional therapeutic intervention: sex therapy, central nervous system agents, and hormonal therapy, guided in part by menopausal status. Sex therapy includes behavior therapy, cognitive behavior therapy, and mindfulness. The only central nervous system agent currently approved by the US Food and Drug Administration (FDA) for HSDD is flibanserin in premenopausal women; use of flibanserin in postmenopausal women with HSDD is supported by data but is not FDA approved. Hormonal therapy includes off-label use of testosterone in postmenopausal women with HSDD, which is supported by data but not FDA approved. The POC incorporates monitoring the progress of therapy. In conclusion, the International Society for the Study of Women's Sexual Health POC for the management of women with HSDD provides a rational, evidence-based guideline for health care professionals to manage patients with appropriate assessments and individualized treatments.

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The International Society for the Study of Women's Sexual Health (ISSWSH) process of care (POC) for hypoactive sexual desire disorder (HSDD) in women provides a consensus management guideline for the diagnosis and treatment of HSDD, the most common sexual dysfunction in women (Figure 1). Given recent research and increasing public awareness about HSDD, greater

numbers of women are anticipated to seek treatment for HSDD from a health care professional (HCP). This POC model consists of an evidence-based approach to identification, diagnosis, and treatment, emphasizing biopsychosocial assessment and education. It highlights opportunities to address modifiable factors, includes patient needs and preferences in the decision-making process, and defines



For editorial comment, 406; for related articles, see pages 429 and 458

Affiliations are at the end of this article.

ARTICLE HIGHLIGHTS

- Hypoactive sexual desire disorder (HSDD), the most common sexual dysfunction in women, has been associated with negative emotional and psychological states, as well as medical conditions including depression; therefore, a guideline for management of HSDD has been developed for health care professionals by the International Society for the Study of Women's Sexual Health.
- This guideline starts with questions to ask regarding sexual health concerns and moves on to diagnosis of generalized acquired HSDD. Treatment begins with education, modification of potentially modifiable factors, and, if needed, additional therapeutic interventions.
- The choice of therapeutic intervention is most often dependent on patient (and partner) preferences and goals.

situations for specialized referral. The model incorporates the following essential principles: (1) identification of subtypes of HSDD, (eg, generalized vs situational and acquired vs lifelong), with emphasis on associated concomitant medical and psychological factors, (2) importance of patient and partner education during all phases of management, (3) goal-oriented focus with patient and partner needs and preferences guiding recommendations for treatment, and (4) clear guidance for follow-up and consideration for referral.

METHODS

This HSDD POC was developed under the auspices of the ISSWSH with input from an international multidisciplinary panel. After a planning conference call, panelists were asked to individually conduct an evidence-based literature review. The panel of 17 researchers and clinicians, ISSWSH members and non-members, convened for 2 days to review and discuss management strategies for HSDD using a modified Delphi method.¹⁻³ This iterative process involved presentations summarizing the current literature, debate and discussion of divergent opinions concerning HSDD assessment and management, and consensus development of a clinical guideline for the HCP. There was no industry participation in any part of the process.

BACKGROUND

Definition of HSDD

Women who are persistently and recurrently not interested in sexual activity who report the absence of sexual fantasies and who are bothered by their lack of sexual interest are said to be experiencing distressing low sexual desire.⁴ Because there is substantial experimental and clinical evidence for this classification,⁴⁻⁸ we will adopt the widely utilized diagnostic label of HSDD to describe women who are distressed by their clinically low levels of sexual desire and utilize the definition developed by the ISSWSH nomenclature committee.⁹ This definition states:

HSDD manifests as *any* of the following for a minimum of 6 months:

- Lack of motivation for sexual activity as manifested by:
 - Decreased or absent spontaneous desire (sexual thoughts or fantasies); or
 - Decreased or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity;
- Loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders;
- And is combined with clinically significant personal distress that includes frustration, grief, guilt, incompetence, loss, sadness, sorrow, or worry.

Hypoactive sexual desire disorder may be lifelong or acquired and generalized or situational. This definition should be understood in a biopsychosocial context and therefore can be applied to both somatic and psychiatric diagnostic schema.⁹

Clinical Significance and Epidemiology

Hypoactive sexual desire disorder is associated with negative emotional and psychological states, as well as medical conditions including depression.¹⁰⁻¹² Women with HSDD may experience decreased quality of life including impaired body image, self-confidence, and self-worth and feel less connected to their partners.¹⁰ Women with HSDD also have increased health care costs and health burden.^{13,14}

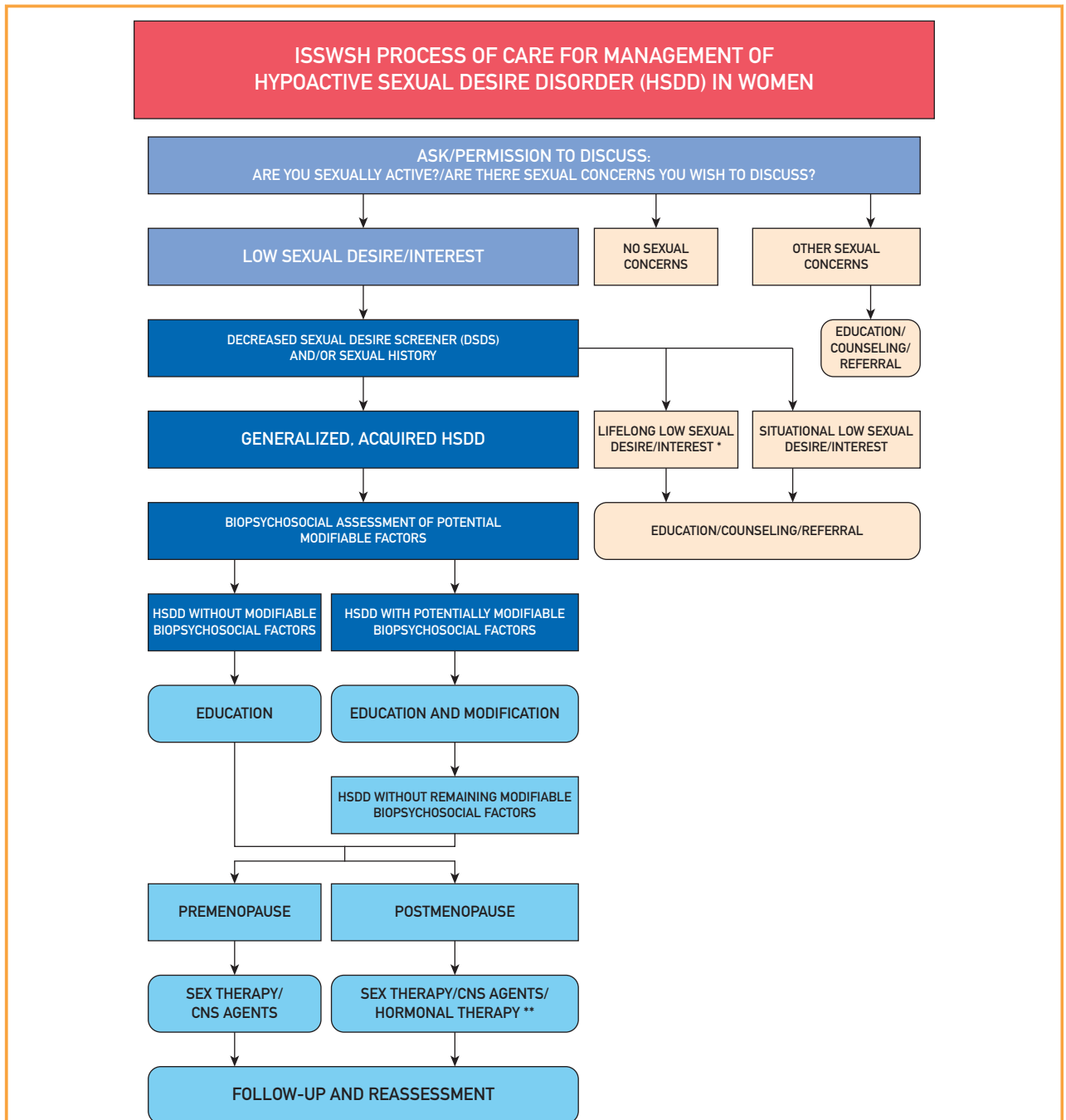


FIGURE 1. The International Society for the Study of Women's Sexual Health (ISSWSH) process of care for hypoactive sexual desire disorder (HSDD) algorithm begins with asking or having permission to discuss sexual concerns and focuses specifically on women who have concerns with their low sexual desire/interest. Initiation of diagnosis starts with the Decreased Sexual Desire Screener or a sexual history. Women with other sexual dysfunctions or those with lifelong or situational low sexual desire/interest are not specifically addressed in this algorithm. Women with generalized acquired HSDD then undergo a focused medical assessment to identify potentially modifiable biopsychosocial factors. Therapeutic intervention begins with education/modification of recognized modifiable factors. Women whose HSDD persists are categorized by menopausal status, and appropriate therapeutic interventions are then followed/reassessed. CNS = central nervous system. *Women with lifelong low sexual desire/interest without distress/bother may characterize themselves as asexual and should not be considered for treatment. **Women in the late reproductive years.

Epidemiologic studies assessing the prevalence of HSDD in women vary according to the (1) definition (low desire/interest; HSDD), (2) group of participants (general population, medical presentation, sex therapy clinics, age group, menopausal status, nationality), and (3) methodology (eg, self-report, interview, questionnaire; face-to-face or online; single-question response, completion of validated scale; inclusion of distress in the definition). These differences in study design have produced prevalence estimates ranging from 17% to over 50%.¹⁵⁻²⁰

In the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study, a widely cited, large population-based survey of 50,001 US women (completers, 31,531; 63% response rate; aged 18-102 years), low desire was the most common sexual problem, reported in 37.7% of participants; low desire with distress (HSDD) was present in approximately 10% of women and was more common than distressing arousal or orgasm difficulties.²¹

Physiology

Sexual desire is regulated by key regions in the brain through the action of various neurotransmitters.²²⁻²⁴ Dopamine, melanocortin, oxytocin, vasopressin, and norepinephrine mediate sexual excitation, whereas opioid, serotonin, endocannabinoid, and prolactin systems mediate sexual inhibition.^{22,23} Although the underlying biological causes of HSDD remain unknown, generalized HSDD likely involves either a predisposition toward inhibitory processes or neuroadaptations that result in decreased excitation, increased inhibition, or a mixture of the two.^{6,25,26} Alterations in brain function and structure may be additionally modulated or reinforced by experience and behavior (experience-based neuroplasticity), further propagating the condition. This perspective is consistent with differential brain activity patterns and structural differences between women with and without HSDD.²⁷⁻³⁰

SCREENING FOR SEXUAL PROBLEMS

The optimal strategy for detecting sexual problems (desire, arousal, orgasm, pain) is “simply to ask” (Figure 1) during the patient visit. The

sexual health interview should be conducted when it feels most natural in the encounter. Begin by asking, “Are you sexually active?” Whether the patient answers “yes” or “no,” continue by asking a direct screening question such as, “Are there sexual concerns you wish to discuss?”⁵ Explain that sexual problems are common and facilitate screening by assuring the patient that you, the physician, are comfortable discussing sexual issues. To normalize and legitimize sexual concerns, you may introduce a direct screening question with a “ubiquity statement” such as, “Many women having [the characteristics of the patient] have concerns about sexual functioning; what about you?”³¹

The start of ubiquity statements may include medical, social, and life-cycle issues such as, “Many women with diabetes...” or “Many women going through menopause...” You may follow the ubiquity statement with an open-ended invitation such as, “Tell me about it.” If a woman reports low desire, it is important to assess the presence of distress related to low desire, which is integral to the definition of HSDD.⁹ If HSDD is present, this POC should be followed. If her sexual problem is arousal, orgasm, or pain, other clinical evaluations and interventions such as education, counseling, or referral should be considered.

DIAGNOSIS

Recommended diagnostic strategies include use of the Decreased Sexual Desire Screener (DSDS) and/or a sexual history to determine the type of HSDD.

Decreased Sexual Desire Screener

The DSDS is a validated instrument for confirming the diagnosis of generalized acquired HSDD in women [*level of evidence (LoE) 2*].^{32,33} The DSDS is brief, effective, user-friendly, and self-completed and requires no special training to administer/interpret (Figure 2).^{34,35} The DSDS serves to grant permission and encourage dialogue for screening for HSDD and identification of etiologic factors, obviating potential patient and physician embarrassment.

The screener includes 5 simple “yes/no” questions. The first 4 incorporate the prerequisites for a diagnosis of generalized acquired

DECREASED SEXUAL DESIRE SCREENER BRIEF DIAGNOSTIC ASSESSMENT FOR GENERALIZED, ACQUIRED HSDD		
THE DECREASED SEXUAL DESIRE SCREENER (DSDS) IS INTENDED TO ASSIST YOUR CLINICIAN IN THE ASSESSMENT OF YOUR DECREASED SEXUAL DESIRE. PLEASE ANSWER EACH OF THE FOLLOWING QUESTIONS BY CIRCLING EITHER YES OR NO.		
1	In the past, was your level of sexual desire or interest good & satisfying to you?	Yes / No
2	Has there been a decrease in your level of sexual desire or interest?	Yes / No
3	Are you bothered by your decreased level of sexual desire or interest?	Yes / No
4	Would you like your level of sexual desire or interest to increase?	Yes / No
5	Please circle all of the factors that you feel may be contributing to your current decrease in sexual desire or interest:	
	a. An operation, depression, injuries, or other medical condition	Yes / No
	b. Medications, drugs, or alcohol you are currently taking	Yes / No
	c. Pregnancy, recent childbirth, menopausal symptoms	Yes / No
	d. Other sexual issues you may be having (pain, decreased arousal or orgasm)	Yes / No
	e. Your partner's sexual problems	Yes / No
	f. Dissatisfaction with your relationship or partner	Yes / No
	g. Stress or fatigue	Yes / No

FIGURE 2. Decreased Sexual Desire Screener. From *J Sex Med*,³² with permission from Elsevier.

HSDD: (1) previous satisfaction with her desire/interest in sex, (2) a decrease from prior satisfaction, (3) bother by the decline in sexual desire, and (4) wish for improvement in her sexual desire.^{26,32} Responses of no previous satisfaction with her desire/interest in sex, and therefore no decrease from prior satisfaction, would be consistent with lifelong low sexual desire/interest. In the fifth query, the patient is asked to identify with “yes/no” responses which, if any, of the 7 listed groups of factors might apply to her situation, potentially having an adverse effect on her sexual desire/interest (Figure 2).³² Low sexual desire and the associated distress and behavioral adaptations may impact the partner relationship, or problems in the partner relationship may contribute to low desire.

If a woman responds “no” to at least 1 of the first 4 questions, she does not meet criteria for generalized acquired HSDD but could meet criteria for either situational or lifelong low

sexual desire/interest. If the patient answers “yes” to questions 1 through 4 and “no” to all the factors in question 5, she has generalized acquired HSDD. If any of the factors in question 5 are present, the HCP must evaluate and consider differential diagnoses including biological etiologies of low desire, as well as decide whether the responses to question 5 indicate generalized acquired HSDD or situational low sexual desire/interest. Situational loss of desire may occur in response to a temporary stressful life situation. Individuals with no/low sexual interest over their lifetime and who are not distressed may be asexual and as such do not meet criteria for HSDD, and no intervention is indicated.³⁶ Comorbid conditions such as arousal and orgasmic disorder do not rule out a concurrent diagnosis of HSDD.

If the DSDS suggests the diagnosis of low sexual interest without distress, distressing lifelong sexual desire, or situational low sexual desire, the HCP should consider strategies that

TABLE 1. Physical Examination to Evaluate Other Factors Contributing to Decreased Desire

Condition	Assessment
Clitoral adhesions/phimosis or clitoral atrophy	Visual examination under magnification
Urethral meatal prolapse, telescoping of urethral meatus	Visual examination under magnification
Vulvodynia	Assess sensitivity to pressure with cotton swab around vestibule from 11-o'clock to 1-o'clock positions
High-tone pelvic floor dysfunction	Manual examination
Labial resorption; vulvar, vestibular, or vaginal atrophy	Visual examination under magnification, vaginal smear (wet mount)
Vulvar dystrophies and dermatoses	Visual examination under magnification, biopsy if needed
Pudendal nerve disorder	Assess tenderness at ischial spine, assess tenderness of pelvic floor muscles
Lumbar-sacral spinal pathology	Quantitative sensory testing, bulbocavernosus reflex latency testing, magnetic resonance imaging of lumbar and sacral spine

engage education and/or counseling or referral to a specialist. In those with generalized acquired HSDD, the HCP may elicit a sexual history or proceed with the POC. In summary, the DSDD offers the HCP a quick, nonthreatening way to screen for and diagnose HSDD in the clinical setting and begin to identify modifiable factors/etiologies.³²

Sexual History

In addition to the DSDD, the HCP may also conduct a sexual history. This may include past and present characteristics of the patient's sexual desire/interest and other aspects of sexual function such as arousal, orgasmic function, and/or any pain/discomfort during sexual activity. Sexual function may be assessed with regard to either partnered or unpartnered sexual activity and may include a history of her past and present partner relationships and sexual experiences. If a sexual desire discrepancy exists between the patient and her partner, it may only be considered HSDD if the desire discrepancy causes her distress.⁹ The evaluation may also include a brief psychosocial assessment because sexual dysfunction may affect the patient's self-esteem and coping ability, as well as her social and occupational role performance.

When a woman endorses distressing low sexual desire, the interview should proceed with questions related to the diagnosis of HSDD including: low motivation for participation in sexual activity, loss of spontaneous sexual desire (including sexual thoughts and

fantasies), lack of desire in response to erotic cues and stimulation, low initiation and avoidance of situations that could lead to sexual activity, and participation in sexual activity due to obligation or fear of losing her partner.²⁶

BIOPSYCHOSOCIAL ASSESSMENT OF POTENTIAL MODIFIABLE FACTORS

For women with a diagnosis of generalized acquired HSDD, HCPs should next obtain a history, perform a physical examination as considered appropriate, and order blood testing when indicated to clarify any modifiable factors.

Physical Examination

A general physical examination of patients who experience HSDD has a low diagnostic yield and does not identify the specific cause of the HSDD in most cases. However, a focused examination, including a pelvic examination with assessment of the vulvar and vaginal tissue, may be appropriate if indicated (Table 1). A physical examination may also reveal signs of hormone insufficiency states.²⁶ The physical examination also provides an excellent opportunity for patient education and reassurance regarding normal genital anatomy. The findings on this examination may be used to identify referral needs.

Laboratory Testing

Laboratory and imaging investigations are dictated by the woman's medical history and physical examination findings. Because there

TABLE 2. Recommended Blood Tests for Further Investigation if HSDD Is Concurrent With Oligomenorrhea or Amenorrhea and/or Galactorrhea

Hormone	Possible conditions	Level of evidence
Prolactin	Hyperprolactinemia causing ovarian suppression and low sex steroid production ^{37,38}	3
Thyroid function panel	Hypothyroidism ³⁹ or hyperthyroidism ⁴⁰	2-3
Estradiol, progesterone, luteinizing hormone, testosterone, sex hormone-binding globulin	Oligomenorrhea or amenorrhea ^{5,37,41}	2-3

are no biomarkers that confirm or exclude HSDD, laboratory testing—specifically, measurement of testosterone—should not be used to make the diagnosis. Other hormone assays may be considered if there is concern about comorbid conditions contributing to low desire, although this testing is not clinically indicated on a routine basis (Table 2).^{5,37-41} These tests are primarily performed to identify specific etiologies or to assess the role of concomitant medical conditions. Referral to a specialist in sexual medicine may be considered if a more specialized physical examination, testing, or treatment is needed. Reasons for referral may include primary/lifelong and/or situational low desire, relationship problems, physical or psychological trauma, endocrinopathy, complex medical problems, or treatment failures.⁴²

When a woman presents with HSDD without any potentially causative comorbidity or relationship conflict, the diagnosis of HSDD without a modifiable cause can be established. In this case, menopausal status should be assessed according to the STRAW + 10 (Stages of Reproductive Aging Workshop) classification system in order to guide therapeutic decision making.⁴³

MODIFIABLE FACTORS

The evaluation for HSDD should include screening for other sexual problems related to arousal, orgasm, and pain⁹ in order to determine the primary vs secondary problem(s) by assessing the temporal relationship of the onset of these complaints relative to the onset of low desire. It is also necessary to determine if HSDD is lifelong or acquired and generalized (occurs in all settings with all partners) or situational. Other key areas of inquiry should include prior sexual functioning and relationship/interpersonal

issues.⁴⁴⁻⁴⁷ It is important to note that a woman can experience HSDD and not be in a stable relationship (ie, has no partner or multiple serial partners).¹⁹

The HCP should ask specifically about other sexual problems that might exacerbate low desire and influence the management and eventual success of treatment. In the Hypoactive Sexual Desire Disorder Registry for Women study, a large observational study of US women with clinically diagnosed generalized acquired HSDD, arousal disorders, lubrication problems, or both were reported by 50.2%, 42.5%, and 39% of women with HSDD, respectively.^{48,49} A list of some potentially useful screeners and questionnaires is provided in the Supplemental Table (available online at <http://www.mayoclinicproceedings.org>).

In patients with generalized acquired HSDD, elicitation of the medical history should include questions about psychiatric conditions, medical problems, and menopausal status (Table 3)⁵⁰⁻⁵³ and relevant medications and misuse/abuse of substances (Table 4).⁵⁴

The assessment should include a medical, psychological, and social history to identify any factors that may be potentially reversible. Obtaining a detailed gynecologic history is important with particular attention to menstrual cycles in premenopausal women; symptoms of the genitourinary syndrome of menopause;⁵⁵ pelvic floor disorders such as urinary incontinence, fecal incontinence, prolapse, and high-tone pelvic floor dysfunction; and menopausal vasomotor symptoms, because each of these factors has been associated with lowered sexual desire.^{15,19,56,57}

Bilateral salpingo-oophorectomy before natural menopause is associated with an increased likelihood of HSDD.¹² Bilateral salpingo-oophorectomy at any age is associated

TABLE 3. Medical Conditions Potentially Impacting Sexual Function^{a,b}

Medical Condition	Desire	Arousal	Orgasm	Pain	Comments
Coronary artery disease	–	+	–	–	None
Hypertension	+	–	–	–	Impact of hypertension or treatment is unclear; one study found an association with low desire
Diabetes	+	–	–	–	Low desire may relate to depression and relationship status
Metabolic syndrome	+	+	+	–	None
Hypothyroidism	–	+	+	–	Increased problems with lubrication and orgasm
Pituitary tumor/hyperprolactinemia	+	–	–	–	None
Urinary incontinence	+	+	–	+	None
Renal failure	–	–	–	–	Dialysis associated with sexual dysfunction
Spinal cord injury/multiple sclerosis/neuromuscular disorders	+	+	+	+	Direct impact on sexual response; indirect effect on desire may be mediated by arousal disorders/pain
Parkinson disease/dementia/head injury	+	–	–	–	Desire may be increased or decreased
Arthritis	–	–	–	+	Decreased mobility and chronic pain may impair sexual function
Dermatological conditions (vulvar lichen sclerosus, vulvar eczema, psoriasis, Paget disease)	–	–	–	+	None
Gynecologic conditions (genitourinary syndrome of menopause, sexually transmitted infections, endometriosis, chronic pelvic pain, childbirth, pelvic organ prolapse)	–	–	–	+	None
Malignancy and treatment (breast, anal, bladder, colorectal, and gynecologic cancers)	+	+	+	+	Sexual function may be directly or indirectly impacted by cancer diagnosis and treatment. Factors include cancer diagnosis, disease itself, treatment (surgery, radiation, chemotherapy), and body image
Major depression	+	+	+	–	None

^a+ = affected; – = not affected.
^bData from references 50-52.
Adapted from *Am Fam Physician*,⁵³ with permission.

with lower total and free testosterone levels.⁵⁸⁻⁶² Women should be asked about other pelvic operations, trauma, or radiotherapy because these factors may be associated with pelvic pain and altered ovarian function. Other conditions associated with lower androgen levels, and potentially diminished desire, include hyperprolactinemia,^{63,64} hypopituitarism, hypothalamic amenorrhea, adrenal insufficiency, primary ovarian insufficiency, and chemical ovarian suppression. Conditions that may increase sex hormone–binding globulin (SHBG) levels, and hence lower free testosterone levels, include hyperthyroidism and human immunodeficiency virus infection.⁶⁵ Overt^{66,68} or subclinical^{66,69} hypothyroidism

and hyperthyroidism have been associated with reduced sexual desire.^{68,70} Conversely, polycystic ovary syndrome is often characterized by clinical and/or biochemical signs of hyperandrogenism, with or without oligoovulation or anovulation, or polycystic ovaries. Women with polycystic ovary syndrome have psychological (feeling less attractive, less feminine, more depressed) and biological (obesity and infertility) factors that may negatively influence their sexual desire.⁷¹

Depressive symptoms are independently and bidirectionally associated with HSDD, with the presence of depression conferring a 50% to 70% increased risk of sexual dysfunction, and the occurrence of sexual dysfunction

is associated with a 130% to 210% increased risk of depression.^{19,72} Adding a layer of complexity, most antidepressants are associated with decreased sexual desire⁷³⁻⁷⁶; therefore, use of antidepressant medication may actually substitute one causative factor of HSDD for another. The Patient Health Questionnaire (PHQ)⁷⁷ is a validated instrument to screen for and monitor severity of depressive symptoms. In the Hypoactive Sexual Desire Disorder Registry for Women study, 34% of a clinical sample of women with acquired, generalized HSDD were found to have concurrent symptoms of depression as measured by the PHQ-9 or were being treated with antidepressant medications; however, 58% had not been diagnosed or treated for depression before entering the study.⁷⁸ In the general population PRESIDE study, 37% of women had concurrent depression as identified either by the PHQ-9, prior diagnosis of depression, or treatment with antidepressant medications.⁷⁹ Given this significant comorbidity, every patient with HSDD should be screened for depressive symptoms because major depressive disorder or treatment with an antidepressant medication may be a modifiable etiologic factor [LoE 2]. It is important to note that depression is also associated with significant chronic medical conditions such as diabetes.⁸⁰

Both type 1 and type 2 diabetes mellitus almost double the risk of sexual dysfunction.⁸¹ In the Epidemiology of Diabetes Interventions and Complications study, 57% of women with type 1 diabetes reported low sexual desire.⁸² Interestingly, the prediabetic state (slightly elevated blood glucose levels) was also characterized by impairment of sexual desire and sexual satisfaction.⁸³ Reduced sexual desire and sexual satisfaction were strongly associated with insulin resistance (Homeostatic Model Assessment Index 1—Insulin Resistance) and therefore susceptible to changes in insulin sensitivity.⁸³

Metabolic syndrome (MetS) is a group of cardiovascular risk factors: high blood pressure, elevated blood glucose level, abnormal cholesterol levels, and abdominal obesity. Data for a relationship between MetS and HSDD are conflicting. In a study of 376 postmenopausal community-dwelling women, those with MetS had significantly lower sexual

TABLE 4. Medications Associated With Female Sexual Dysfunction

Medication	Desire disorder	Arousal disorders	Orgasm disorders
Anticholinergics	–	+	–
Antihistamines	–	+	–
Amphetamines and related anorexic drugs	–	–	+
Cardiovascular and antihypertensive medications			
Antilipid medications	+	–	–
β-Blockers	+	–	–
Clonidine	+	+	–
Digoxin	+	–	+
Spironolactone	+	–	–
Methyldopa	+	–	–
Hormonal preparations			
Danazol	+	–	–
GnRH agonists	+	–	–
Hormonal contraceptives	+	+	–
Antiandrogens	+	+	+
Tamoxifen	+	+	–
GnRH analogues	+	+	–
Ultralight contraceptive pills	+	+	–
Narcotics	+	–	+
Psychotropics			
Antipsychotics	+	+	+
Barbiturates	+	+	+
Benzodiazepines	+	+	–
Lithium	+	+	+
SSRIs	+	+	+
TCA	+	+	+
MAO inhibitors	–	–	+
Venlafaxine	+	+	+
Other			
Histamine 2 receptor blockers and promotility agents	+	–	–
Indomethacin	+	–	–
Ketoconazole	+	–	–
Phenytoin sodium	+	–	–
Aromatase inhibitors	+	+	–
Chemotherapeutic agents	+	+	–

GnRH = gonadotropin-releasing hormone; MAO = monoamine oxidase; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; + = yes; – = no. Adapted from *Fertil Steril*,⁵⁴ with permission from Elsevier.

desire compared with other women.⁸⁴ Three smaller case-control studies did not find any significant association between MetS and sexual desire.⁸⁵⁻⁸⁷ Whereas in population-based studies sexual desire is inversely associated with body mass index,⁸⁸⁻⁹⁰ 3 clinical studies of women seeking or undergoing weight loss treatment did not find an increase in sexual desire.⁹¹⁻⁹³ However, observational studies have consistently indicated a trend toward improvement in sexual desire after weight loss,^{94,95} potentially due to improved body image. Both obesity and MetS have been

associated with increased baseline clitoral vascular resistance and impaired sexual arousal, suggesting that the negative impact of these metabolic phenotypes on sexual function is primarily at the genital level rather than a central effect.⁹⁶

Various neurologic diseases have been associated with decreased sexual desire, notably multiple sclerosis^{97,98} and spinal cord injury,⁹⁹ but data are limited.

Decreased sexual desire is a common issue for women after a diagnosis of breast cancer, ranging from 23% to 80% of women.^{100,101} Sexual problems are independently associated with being postmenopausal (potentially provoked by chemotherapy), having vasomotor symptoms, and taking an aromatase inhibitor (AI).^{101,102} Chemotherapy increases the likelihood of sexual complaints compared with surgery and/or radiation.¹⁰³ In addition, AI therapy is associated with vaginal dryness, dyspareunia, and decreased sexual desire.^{102,104}

Medications that lower testosterone production include combined hormonal contraceptives (CHCs; oral, transvaginal, and transdermal),¹⁰⁵ chemical ovarian suppression by gonadotropin-releasing hormone analogues, and pharmacological glucocorticoid administration. Some other compounds exhibit antiandrogen activity (spironolactone, cyproterone acetate, flutamide, and finasteride). Drugs increasing SHBG levels, and hence lowering free testosterone levels, also include oral estrogens, CHCs, tamoxifen, and thyroxine.⁶⁵ A double-blind, placebo-controlled, randomized trial determined that a levonorgestrel-containing oral contraceptive lowers sexual desire in comparison with placebo.¹⁰⁶ Even though all CHCs suppress ovarian testosterone production, the greatest increase in SHBG level is seen with the higher ethinyl estradiol doses (30-35 µg) and with third- or fourth-generation progestins.¹⁰⁵ A recent study found evidence for a role of the CAG repeat length of the androgen receptor on the sexual desire of contraceptive users.¹⁰⁷ In addition, drugs that may elevate prolactin levels and, in part, decrease sexual desire include antipsychotics and others.^{38,108} We conclude that CHCs may be associated with HSDD in some women, and thus, change of medication may improve desire [LoE 2].

TREATMENT

Therapeutic strategies for this POC include education and, if needed, addressing modifiable factors. Should generalized acquired HSDD persist, treatment may include sex therapy, central nervous system (CNS) agents, and hormonal agents, taking into account menopausal status.

First- and Second-Line Therapies

Education. Effective patient education requires knowledge, time, communication skills, and bibliographic resources that facilitate positive sexual behavioral changes.⁴³ Education may be structured in 3 parts. First, provide information on normal sexual functioning. This information may include a description of spontaneous and responsive sexual desire, the role of motivation in sexual desire, the importance of adequate sexual stimulation, the impact of pleasurable sexual experiences on desire, and the influence of age and relationship duration.¹⁰⁹⁻¹¹¹ Second, educate the patient about factors that are derived from the sexual and medical history that may disrupt sexual desire (eg, mood disorders, relationship satisfaction, body image).⁵ Third, HCPs may assess motivation for treatment and discuss treatment options.^{5,112} If the patient has a partner, involving the partner in treatment may sometimes be helpful. Education should continue throughout the process, including patient follow-up.

Modification of Potentially Contributing Factors.

The next intervention level includes modification of factors thought to be playing a role in HSDD. The following paragraphs summarize strategies for intervention for some of the more common modifiable factors associated with HSDD and are based on consensus expert opinion.

Treatment of genital arousal symptoms and pain with vaginal lubricants, vaginal moisturizers, low-dose vaginal estrogen or intravaginal dehydroepiandrosterone (DHEA),¹¹³ or physical therapy (for hypertonic, tender pelvic floor muscles)^{114,115} and menopausal vasomotor symptoms with systemic hormone therapy¹¹⁶ may relieve symptoms and therefore improve desire. In particular, pain with sexual activity should be addressed before treatment of HSDD.

In women with type 2 diabetes, limited evidence suggests that lifestyle modifications that include substantial weight loss may

TABLE 5. Psychological Factors and Treatment Strategies

Psychological factor	Recommended approach
Depression/anxiety	Pharmacotherapy/cognitive behavioral therapy
Poor self-esteem/body image	Psychotherapy
Stress/distraction	Cognitive behavioral therapy
History of abuse (physical, sexual, emotional)	Psychotherapy
Substance abuse	Psychotherapy
Self-imposed pressure for sex	Office-based counseling or refer for cognitive behavioral therapy
Religious, personal, cultural or family values, beliefs, and taboos	Office-based counseling or refer for cognitive behavioral therapy
Relationship factors	Office-based counseling or refer for individual/couples therapy
Lifestyle factors (eg, fatigue, sleep deprivation)	Office-based counseling
Sexual factors (eg, inadequate stimulation)	Office-based counseling

alleviate sexual dysfunction.³⁷ Treatment of gynecologic disorders and urinary or fecal incontinence may positively impact sexual desire.^{50,51} Malignant disorders may adversely affect sexual function either directly, as the result of the disorder itself, or indirectly, related to the cancer diagnosis or treatment, and addressing sexual changes resulting from cancer or treatment may lead to improved sexual function.¹¹⁷

Sleep problems and insomnia in particular are common concerns among women. In the Women's Health Initiative Observational Study, higher insomnia scores and shorter durations of sleep (<7-8 hours) were associated with decreased sexual function.¹¹⁸ Improving duration and quality of sleep may positively affect sexual function.

As noted previously, depression has a bidirectional association with sexual dysfunction, and adequate treatment of depression may positively impact sexual function.^{5,72} Additionally, antidepressant medications are commonly associated with treatment-emergent sexual dysfunction, a potential adverse effect that may result in discontinuation of treatment and impaired quality of life.^{75,119,120} Management strategies for antidepressant-related sexual dysfunction include behavioral (eg, exercise, scheduling sexual activity, vibratory stimulation),^{121,122} complementary (eg, acupuncture),¹²³ and pharmacological (eg, dose reduction or discontinuation, switching to a drug with fewer sexual adverse effects, and adding antidotes/adjunctive treatment) therapies.¹²⁴⁻¹²⁷ Other commonly used medications potentially impacting sexual function include CHCs, AIs, and spironolactone.⁵⁴ Reviewing a patient's medication list

and modifying medication regimens potentially impacting sexual function (Table 4) may improve sexual desire. Alcohol, smoking and illicit substance use may also contribute to sexual dysfunction.

Several psychological factors that may contribute to loss of sexual desire may be modifiable. Table 5 lists the most common psychological factors contributing to HSDD. Relationship factors frequently adversely impact sexual desire. Health care professionals may use office-based counseling or may consider referring the patient to an individual or couples therapist to modify negative communication patterns, to address partner sexual dysfunction, to modify the partner's pressure or demanding behavior for sex, and to help problem solve when lack of time and/or privacy are contributing factors.⁵¹ Office-based counseling may also be useful to reevaluate and alter interfering beliefs and values¹²⁸ and should be continued in follow-up.

Third-Line Treatment Options

Sex Therapy. A range of psychological interventions has been developed to treat sexual dysfunctions in women, independent of menopausal status. Focused sex therapy for HSDD is unlikely to be effective if relationship problems contributing to low desire or as a result of HSDD (ie, power, control, trust) for women with a partner, sexual dysfunction in the partner, or a history of sexual, physical, or emotional abuse are not addressed.

Three frequently used psychological interventions are behavior therapy, cognitive behavior therapy (CBT), and mindfulness therapy. Behavior therapy attempts to alleviate

sexual difficulties through a combination of techniques including education, communication skills training, and sensate focus exercises.^{129,130} On their own, sensate focus exercises are unlikely to be effective for HSDD in women [LoE 5].

Cognitive behavior therapy is designed to challenge unrealistic beliefs that may be contributing to sexual problems and to alter behaviors that maintain HSDD. For example, individuals may be making cognitive errors, personalizing, or catastrophizing.¹³¹ With the help of the therapist, the patient learns to identify and challenge the unrealistic beliefs that trigger negative behaviors and emotions regarding sexual activity. A meta-analysis of 20 small studies using psychological interventions vs a wait-list control in multiple settings in the treatment of various types of sexual dysfunctions in men and women (4 of the 20 studies were of HSDD in women)¹³² found that psychological interventions were effective in reducing symptom severity and, to a lesser degree, improving sexual satisfaction among women with low sexual desire [LoE 1]. A more recent, more specific review¹³³ found 3 studies in which CBT in women with HSDD was effective vs wait-list controls.

Mindfulness-based CBT includes exercises that aim to cultivate present-moment awareness and nonjudgmental observation of experiences.¹³⁴⁻¹³⁶ When applied to HSDD, mindfulness exercises may help decrease cognitive distraction during sexual activity and increase awareness of pleasurable sensations.¹³⁶⁻¹³⁹ Two wait-list controlled studies support mindfulness meditation training in women with HSDD.¹³³ To date, 5 studies have evaluated the incorporation of mindfulness training into a CBT intervention for women with non-HSDD female sexual problems¹⁴⁰⁻¹⁴⁴ and found improvements in sexual desire and related distress. Mindfulness therapy has demonstrated preliminary levels of effectiveness in the treatment of this disorder among women.¹⁴⁴⁻¹⁴⁶

CNS Agents. Flibanserin is currently the only US Food and Drug Administration–approved medication for generalized acquired HSDD in premenopausal women. Flibanserin (100 mg dosed at bedtime) is a nonhormonal, centrally acting, daily, oral, multifunctional serotonin

agonist and antagonist.¹⁴⁷ Efficacy was established in 3 pivotal trials in more than 3500 women, demonstrating a statistically significant and clinically meaningful improvement in the level of sexual desire and the number of sexually satisfying events and a decrease in distress compared with placebo [LoE 1].¹⁴⁸⁻¹⁵⁰

Clinical trials of flibanserin in postmenopausal women have found similar efficacy, but it is not currently Food and Drug Administration–approved in this population.¹⁵¹ Approximately 50% of women with HSDD respond to flibanserin, and it may take up to 8 weeks for efficacy to emerge. The most common adverse events (AEs) in premenopausal women are dizziness (9.2%), somnolence (8.3%), nausea (6.5%), and fatigue (3.7%)¹⁴⁷; placebo-corrected rates are similar to other CNS-active agents. Most AEs are mild, transient, and mitigated with bedtime dosing. In the trials, discontinuation due to AEs was 13% in premenopausal women treated with flibanserin compared with 6% with placebo.

Flibanserin labeling has a boxed warning that concomitant alcohol use is contraindicated on the basis of the results of an alcohol challenge study that found an increase in sedation, syncope, and hypotension in the treatment group (23 men and 2 women).¹⁵² However, alcohol use was not restricted and did not increase such AEs over placebo in the 3 major pivotal trials that were limited to premenopausal women.¹⁵³ A postapproval alcohol interaction study performed in 96 women (≤ 45 years old) revealed no effect of concomitant ethanol ingestion for somnolence, drowsiness, orthostatic blood pressure, vertigo, or hypotension with no reports of syncope, although a small increase in dizziness was reported at the highest dose of ethanol (0.6 g/kg) when taken with flibanserin (39.8%) compared with flibanserin alone (31.3%).¹⁵² A risk evaluation and mitigation program requires certification of prescribers and pharmacies in consenting patients to avoid alcohol.

Other CNS-active agents approved for other indications have been used off-label for the treatment of HSDD despite limited efficacy and safety data. Bupropion, which acts to enhance dopamine and norepinephrine, was found in a randomized, double-blind, placebo-controlled trial (at 300-400 mg/d) to improve sexual desire vs placebo in women

with HSDD, but enrollment was insufficient to reach statistical significance, as prespecified in the study protocol [LoE 2].¹⁵⁴ Adverse effects of bupropion used for treatment of major depression or smoking cessation include tremor (13.5%), agitation (9.7%), dry mouth (9.2%), constipation (8.2%), dizziness (6.1%), and nausea/vomiting (4%).¹⁵⁵ In women with antidepressant-induced sexual dysfunction, the addition of sustained-release bupropion (300 mg/day) improved sexual desire vs placebo.¹²⁵

Buspirone, which reduces serotonin inhibition, is another off-label treatment that has been used for antidepressant-associated sexual dysfunction. One trial found improvement in sexual function (including “low libido”) in depressed women with selective serotonin reuptake inhibitor–induced sexual dysfunction with buspirone (30–60 mg/d) compared with placebo (58% vs 30%) [LoE 2].^{6,156} The most common adverse effects of buspirone in studies of generalized anxiety disorder (approved indication) are dizziness (9%), nervousness (4%), nausea (3%), and headache (3%).

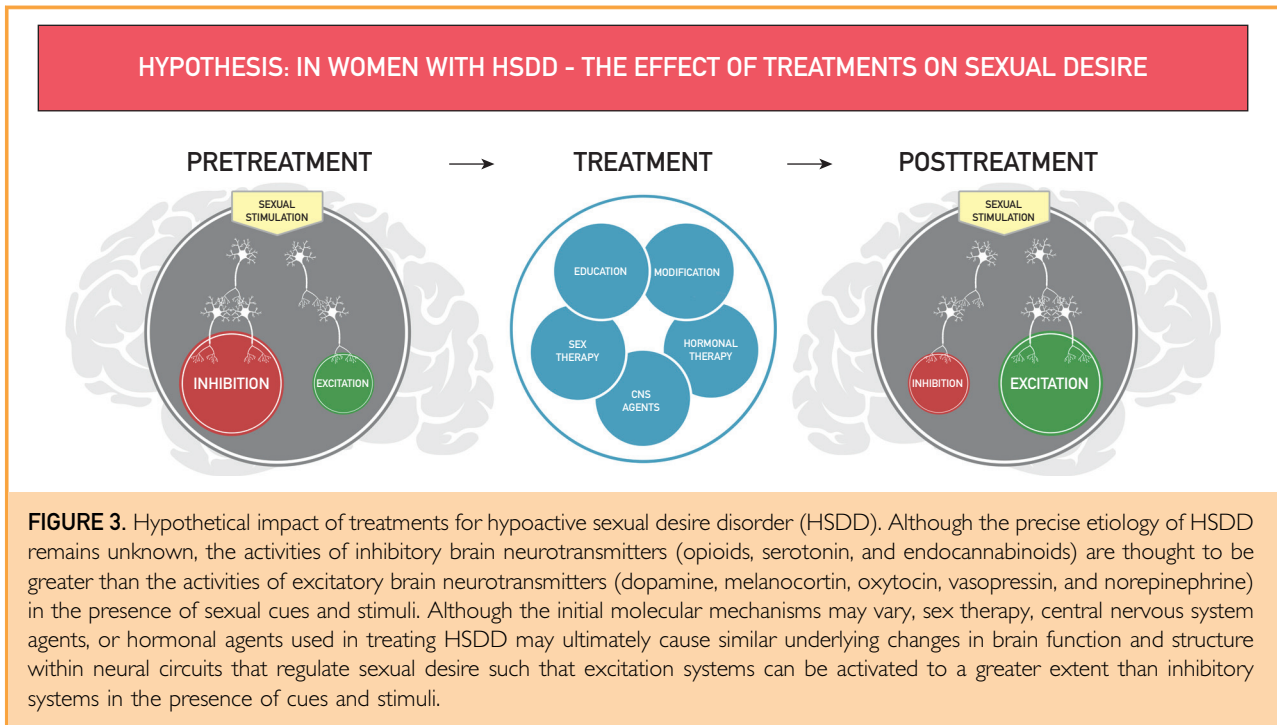
Drug development research for HSDD has been directed toward finding CNS agents that specifically activate stimulatory pathways or reduce inhibitory pathways regulating sexual desire.¹⁵⁷ Therapies in clinical trial development include bremelanotide^{158–164} and combination therapies: testosterone with sildenafil and testosterone with buspirone^{165–167} and bupropion with trazodone.¹⁶⁸

Hormonal Therapy. Testosterone therapy was initially approved in Europe for the treatment of HSDD in surgically menopausal women and is currently approved in Australia for women with testosterone deficiency and associated symptoms such as low sexual desire. However, testosterone therapy in women remains an off-label treatment in other countries. Oral testosterone therapy is not recommended because there are substantial intraindividual and interindividual variations in absorption such that levels achieved are often supraphysiologic and may result in lipid/cardiac effects and hepatotoxicity.¹⁶⁹ Studies using transdermal testosterone have consistently revealed efficacy for the treatment of HSDD in both naturally and surgically

postmenopausal women, either alone or in combination with menopausal estrogen therapy [LoE 1].^{26,65,170} Four published 24-week phase 3 clinical trials in naturally and surgically postmenopausal women with HSDD found that a 300- μ g/d testosterone patch significantly improved the primary efficacy measures of sexual desire and frequency of satisfying sexual events (measured by proprietary instruments) vs placebo.^{171–174} Levels of sexually related distress also decreased significantly compared with placebo in 3 of the 4 studies.

The most common AEs in descending order were application site reactions, acne, breast pain, headache, and hirsutism. Laboratory findings (liver function and hematologic tests, lipid profiles, clotting measures, and carbohydrate metabolism) remained essentially unchanged from baseline and did not differ among treatment groups.^{171–176} In postmenopausal women, when serum free testosterone is maintained within the normal range for premenopausal women, short-term safety data are reassuring [LoE 1].^{170,177,178} However, the long-term safety of testosterone use in postmenopausal women is limited to observational studies.¹⁷⁹ Likewise, long-term (beyond 2 years) safety data with regard to breast cancer and cardiovascular events are limited to observational trials and are inconclusive.^{171,176,179,180} Studies involving reproductive-aged women are lacking.

If testosterone therapy is being considered (at the discretion of the patient and the HCP), baseline and follow-up testosterone values may be assessed [LoE 2–3].²⁶ Normal testosterone ranges have been reported for women of different age groups, but there is no minimal value for any androgen that can be used to identify women with HSDD.^{65,181} Most circulating testosterone is bound to proteins (ie, SHBG, albumin), and only 1% to 2% of the total testosterone is unbound or free and biologically active.⁶⁵ Sex hormone–binding globulin levels vary considerably among individuals⁵⁸ and may be increased by oral estrogens, hormonal contraception, and thyroid hormone replacement and lowered by central adiposity and oral androgen therapy.^{181,182} Most radioimmunoassays lack the precision to accurately measure total testosterone levels in women¹⁸³ such that, when possible, testosterone should be measured by liquid



chromatography—mass spectrometry, which is increasingly becoming available to clinicians.¹⁸⁴ Free testosterone levels can be calculated from measured total testosterone and SHBG levels using an online calculator.¹⁸⁵ Women using testosterone should have regular follow-up blood testosterone measurements to ensure that supraphysiologic therapy is avoided.¹⁷⁰

Testosterone formulations for women are not globally available, so clinicians are commonly limited to prescribing compounded formulations or testosterone formulations for men modified to much lower administered doses (usually one-tenth of the male dose) because supraphysiologic concentrations can cause virilization [LoE *Expert opinion/clinical principle*].^{65,170} When a trial of testosterone therapy is initiated, treatment should be discontinued if the patient experiences no improvement in symptoms after 6 months.¹⁷⁰

The synthetic orally active steroid tibolone is weakly androgenic and lowers SHBG, resulting in an increase in endogenous free testosterone.¹⁸⁶ Although a small randomized clinical trial of women with sexual dysfunction found tibolone to be marginally more effective for low desire than transdermal hormone

therapy,¹⁸⁷ a recent meta-analysis failed to confirm tibolone's benefit on sexual desire in postmenopausal women [LoE 2-3].¹¹⁶

Concerning oral DHEA, systematic reviews and meta-analyses have found no statistically significant benefit of systemic DHEA on female sexual dysfunction [LoE 1].¹⁸⁸

Follow-up and Reassessment

Reassessment and follow-up should be conducted at regular intervals at the discretion of the HCP. This step facilitates patient communication including discussion regarding other problems, patient concerns regarding treatment (eg, adverse drug reactions), and other sexual dysfunctions such as pain, partner issues, or lifestyle factors such as emotional distress. Patients may change medication regimens for other conditions that may impact treatment of HSDD. The need for dosage titration or substitution of one therapy for another may be considered at each follow-up visit. Patients may change treatment preferences, seek new information, or wish to reevaluate their current treatment regimen. Lastly, general medical and psychosocial reassessment should occur at regular intervals, depending on the health and

psychosocial needs of the patient. Follow-up is intended to monitor the progress of therapy and the medical status of the patient (and partner) and provides an opportunity for further patient education.

DISCUSSION

The management steps within this POC are dependent on first asking about sexual health concerns, then distinguishing among the sexual dysfunctions to identify women with HSDD, and finally making the appropriate selection of treatment options. Treatments may include education, addressing potentially modifiable factors, psychological therapy, CNS agents, or hormone therapy. Management principles include taking into account risk to benefit ratio, degree of invasiveness, and cost in order to provide individualized care. The final decision with regard to treatment is most often dependent on patient (and partner) preferences and goals. This factor is clinically relevant considering the lack of comparison data to prioritize these therapies for HSDD.

Although the precise mechanisms for any given treatment may vary, we hypothesize that all effective treatments for HSDD result in functional changes in the neural pathways regulating sexual desire in order to enable excitation to overcome inhibition in the appropriate context of spontaneous sexual thoughts and/or visual/aural/physical stimulation (Figure 3). This hypothesis is consistent with studies demonstrating neuroplastic alterations regulating neurogenesis, synaptic plasticity, and synaptic activity associated with all of the recommended interventions: mindfulness and cognitive behavioral therapy,¹⁸⁹⁻¹⁹² steroid hormones,^{193,194} and CNS-active drugs that modulate the neurotransmitter systems mediating HSDD.¹⁹⁵⁻¹⁹⁷

Given the unmet need of women with HSDD, developmental efforts are continuing for new safe and effective treatments. However, cost of development and regulatory requirements remain substantial obstacles. It should be emphasized that the impact of any drug therapy is not to circumvent the inhibitory influence on sexual desire that normally predominates. Rather, modulation of neuroendocrine systems may facilitate the activation of

sexual desire pathways when both physiologic stimulation and social context are sufficient and appropriate.

This ISSWSH POC is an international consensus guideline to help HCPs in the management of women with HSDD. Health care professionals are encouraged to initiate a conversation with their patients about sexual activity and sexual satisfaction. Asking about these issues using the techniques noted in this POC can demonstrate a deeper interest on the part of the HCP in aspects of life that may be extremely important to patients. The depth of the inquiry can depend on the interests and depth of experience of the HCP. Self-recognition of an HCP's clinical and practice limitations can result in appropriate referral of a woman for a distressing problem, both empowering the patient and leading to successful outcome.

CONCLUSION

The ISSWSH POC provides guidelines for clinicians caring for women to diagnose HSDD and provide management, taking into account all the contributing biopsychosocial aspects: physical, medical, and medication factors; relationship and life situations; and personal sexual behaviors and history in order to provide education, modification of existing factors, and treatment based on shared decision making between the patient and her HCP. The ultimate goal of all treatment programs is improved function via a working partnership between the patient and her HCP.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AE** = adverse event; **AI** = aromatase inhibitor; **CBT** = cognitive behavior therapy; **CHC** = combined hormonal contraceptive; **CNS** = central nervous system; **DHEA** = dehydroepiandrosterone; **DSDS** = Decreased Sexual Desire Screener; **HCP** = health care professional; **HSDD** = hypoactive sexual desire disorder; **ISSWSH** = International Society for the Study of Women's Sexual Health; **LoE** = level of evidence; **MetS** = metabolic syndrome; **PHQ** = Patient Health Questionnaire; **POC** = process of care; **SHBG** = sex hormone-binding globulin

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